PROGNOSTIC FACTORS AND OUTCOMES AFTER LIVER RESECTION FOR HEPATOCELLULAR CARCINOMA IN NON-CIRRHOTIC, NON-FIBROTIC LIVER

Dissertation submitted to

THE TAMILNADU DR.M.G.R.MEDICAL UNIVERSITY

In partial fulfillment of

the requirements for the degree of

M.Ch (SURGICAL GASTROENTEROLOGY & PROCTOLOGY)

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GOVT.STANLEY MEDICAL COLLEGE & HOSPITAL,

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY

CHENNAI, INDIA

AUGUST 2013

CERTIFICATE

This is to certify that this Dissertation entitled **"PROGNOSTIC FACTORS AND OUTCOMES AFTER LIVER RESECTION FOR HEPATOCELLULAR CARCINOMA IN NON-CIRRHOTIC, NON-FIBROTIC LIVER"** is the bonafide original work of **Dr. M.SATISH DEVAKUMAR**, in partial fulfillment of the requirement for **M.Ch., (Branch VI) Surgical Gastroenterology & Proctology** examination of the Tamilnadu Dr.M.G.R Medical University to be held in AUGUST 2013. The period of study is from August 2010 to December 2012.

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DECLARATION

I, **Dr. M. SATISH DEVAKUMAR,** solemnly declare that the dissertation titled **"PROGNOSTIC FACTORS AND OUTCOMES AFTER LIVER RESECTION FOR HEPATOCELLULAR CARCINOMA IN NON-CIRRHOTIC, NON-FIBROTIC LIVER"** is the bonafide work done by me at Govt. Stanley Medical College & Hospital during August 2010 to December 2012 under the expert guidance and supervision of **Prof. G. MANOHARAN, MS., MCh.,** Professor and Head, Institute of Surgical Gastroenterology & Liver transplantation, Stanley Medical College,Chennai-600001.

The dissertation is submitted to the **Tamil Nadu Dr. M.G.R Medical University,** towards partial fulfillment of requirement for the award of **M.ch., Degree (Branch - IV) in Surgical Gastroenterology & Proctology.**

Place: Chennai

Date: March 2013 **(Dr.M.SATISH DEVAKUMAR)**

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Dr. M. SATISH DEVAKUMAR

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Title of the Work : Prognostic factors and outcomes after liver resection for Hepataocellular Carcinoma in Non-Cirrhotic, Non-Fibrotic Liver

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Department : Department of Surgical Gastroenterology Government Stanley Medical College, Chennai-1

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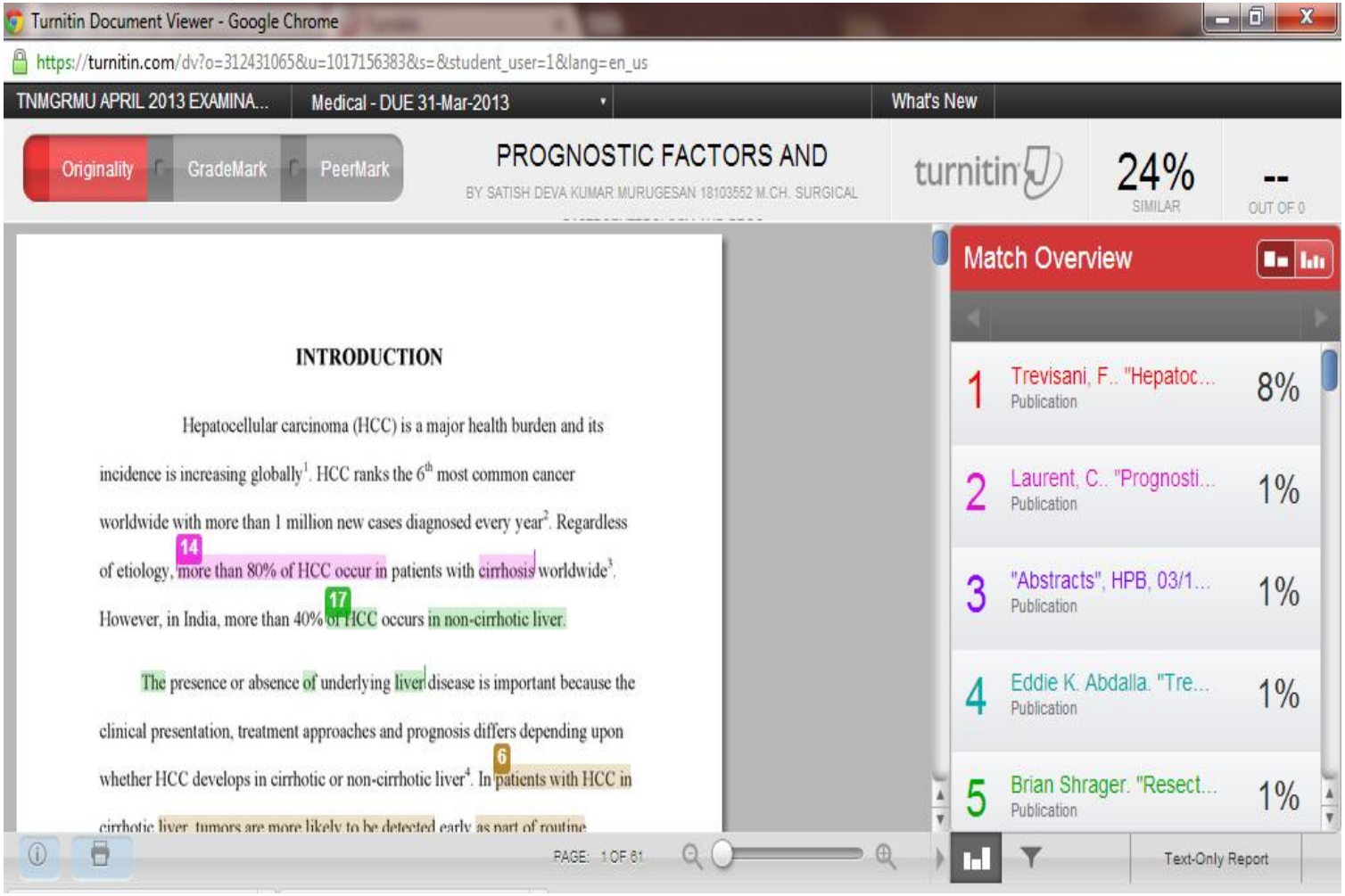
INTRODUCTION Hepatocellular carcinoma (HCC) is a major health burden and its incidence is increasing globally1. HCC ranks the 6th most common cancer worldwide with more than 1 million new cases diagnosed every year2. Regardless of etiology, more than 80% of HCC occur in patients with cirrhosis worldwide3. However, in India, more than 40% of HCC occurs in non-cirrhotic liver. The presence or absence of underlying liver disease is important because the clinical presentation, treatment approaches and prognosis differs depending upon whether HCC develops in cirrhotic or non-cirrhotic liver4. In patients with HCC in cirrhotic liver, tumors are more likely to be detected early as part of routine...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Hepatocellular carcinoma (HCC) is a major health burden and its incidence is increasing globally[1]. HCC ranks the 6th most common cancer worldwide with more than 1 million new cases diagnosed every year[2]. Regardless of etiology, more than 80% of HCC occur in patients with cirrhosis worldwide[3]. However, in India, more than 40% of HCC occurs in non-cirrhotic liver.
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INTRODUCTION

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Hepatocellular carcinoma (HCC) is a major health burden and its incidence is increasing globally.[1] HCC ranks the 6thmost common cancer worldwide with more than 1 million new cases diagnosed every year.[2] Regardless of etiology, more than 80% of HCC occur in patients with cirrhosis worldwide.[3] However, in India, more than 40% of HCC occurs in non-cirrhotic liver.

The presence or absence of underlying liver disease is important because the clinical presentation, treatment approaches and prognosis differs depending upon whether HCC develops in cirrhotic or non-cirrhotic liver.[4] In patients with HCC in cirrhotic liver, tumors are more likely to be detected early as part of routine screening and hence are treated by more minor intervention or by liver transplantation. Conventional liver resection is rarely performed in patients with HCC in cirrhotic livers, owing to the risk of post-hepatectomy liver failure.[5] In contrast, patients with non-cirrhotic liver present at later stage with large tumors and are usually treated by major liver resection due to high rate of recurrence in transplanted liver.[6,7]

Although multiple treatment modalities have been established for HCC over the past decades, surgery – liver resection or transplantation -

gives the best chance of long term survival and cure.[8] In general, the role of liver transplantation for non-cirrhotic patients with HCC is not clear because they usually fall outside the current transplantation criteria, issue of organ shortage, associated with high rate of recurrence in transplanted liver and high mortality rate of up to 25% among patients on the transplant wait list. Moreover, transplantation for HCC in non-cirrhotic liver has no additional benefit of improving the patient's long term liver function.[9]Several studies have shown that hepatic resection can offer optimal therapy for non-cirrhotic patients with HCC. However, intrahepatic recurrence after curative resection of HCC is unacceptably high in non-cirrhotic patients. Therefore, in order to improve the surgical outcomes in these patients, it is of paramount importance to identify the prognostic factors for survival and the risk factors for intra-hepatic tumor recurrences after curative resection for HCC in non-cirrhotic liver.[10]

The alternative treatment options, such as trans-arterial chemoembolization (TACE) and radiofrequency ablation (RFA), are limited by lack of complete tumor eradication and are clearly not suitable for such large tumors in non-cirrhotic HCC patients.

The significant improvements in diagnostic imaging, surgical techniques and post-operative care have shown very low operative

mortality in the experienced centers.[11]Despite these advances, the long term prognosis of patients with HCC is dismal. Numerous publications have addressed the prognostic factors and long term survival after liver resection for HCC, but most of these studies have included patients with and without cirrhosis.[12-16] The prognostic factors for survival or the risk factors for tumor recurrence in patients undergoing liver resection for HCC in non-cirrhotic liver is not well documented.[17]Data analyzing the outcomes of liver resection for HCC in patients with non-cirrhotic liver is also limited.[4]

AIMS OF THE STUDY

AIM OF THE STUDY

The aim of the present study was:

1. To compare the clinic-pathological and technical factors between patients with HCC in non-cirrhotic, non-fibrotic liver and that in cirrhotic liver.

2. To evaluate the peri-operative and short-term outcomes after liver resection for HCC in non-cirrhotic liver.

3. To identify predictive factors and outcome after liver resection for non-cirrhotic HCC.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Hepatocellular Carcinoma (HCC) is the most common primary malignant tumor in the adult liver.[18] HCC is the sixth most common cancer with 749,000 new cases per year and accounts for 7% of all new cancer diagnosed worldwide.[19]It is a deadly malignancy and the 3rdcause of cancer related death with 692,000 deaths worldwide per year.[18]

The global distribution of HCC presents marked geographical variation. According to age-adjusted incidence rate (AAIR) per 100,000 population per annum, the different geographical regions of HCC can be divided into three incidence zones: Low (<5), intermediate (between 5 and 15), high (>15).[20] Most Asian countries, including India are in the intermediate or high incidence zone for HCC.[21]

Several registries have shown that the HCC incidence rates have changed during the past several years. Hepatitis B virus vaccination and improvements in health standards have decreased the incidence rate in some high risk areas such as Taiwan and Japan. In contrast, HCC incidence is increasing in the United States and India, probably reflecting the different timing in the appearance of risk factors.[18] In India, the four population based registries at Chennai, Bangalore, Mumbai and Delhi have shown statistically significant increase in

incidence of liver cancer (Figure 1). The annual percent change (APC) was 1.6 for Chennai and Delhi, 2.0 for Bangalore and 2.6 for Mumbai. The average incidence of HCC in India is 2.7% for males and 1.3% for females.[22,23]

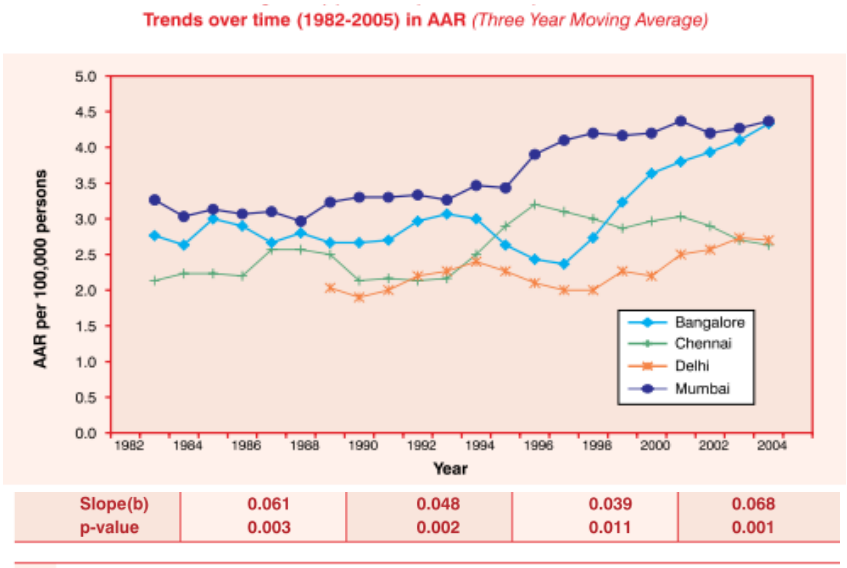


Figure 1: The incidence of HCC in the four population based registries at Chennai, Bangalore, Mumbaiand Delhi

Worldwide, up to 90% of HCC are associated with cirrhosis, [24,25-28] however in India, up to 40% of HCC occurs in non-cirrhotic liver.

DEMOGRAPHIC CHARACTERISTICS:

Most studies regarding non-cirrhotic liver have demonstrated equal sex distribution (male/female ratio: 1.3-2: 1) when compared with cirrhotic counterpart with male predominance (male/female ratio: 3.2 to

8:1).[26,27] The mean age at presentation in non-cirrhotic is about 10 year lower thanin cirrhotic patients.[11,29]

ETIOLOGICAL FACTORS:

1. Chronic viral hepatitis:

Hepatitis B virus (HBV) or C virus (HCV) chronic infections are the major risk factors in non-cirrhotic HCC, as seen in cirrhotic patients with HCC. Table-1and 2 shows the prevalence of HBV surface antigen (HBsAg) positive and anti-HCV antibody positive status in cirrhotic and non-cirrhotic patients with HCC coming from different geographical areas.

Table 1: The reported prevalence of HBsAg positive status in non-cirrhotic and cirrhotic patients with hepatocellular carcinoma (HCC) in the literature.

Reference	HBsAg positive status		p-value
	Non-cirrhotic HCC patients (%)	Cirrhotic HCC patients (%)	
Trevisani et al[26]	10/102 (9.8%)	81/360 (22.5%)	0.007
Nzeako et al[27]	17/342 (5.0%)	43/462 (9.3%)	<0.05
Bralet et al[49]	11/80 (13.7%)	79/250 (31.6%)	0.003
Shimada et al[29]	7/65 (10.8)	102/450 (22.7%)	0.034
Grazi et al[11]	17/135 (12.6%)	46/308 (14.9%)	n.s
Chang et al[9]	142/221 (64.3%)	150/217 (69.1%)	n.s
Kumar et al[112]	26/52 (50.0%)	85/137 (62.0%)	n.s

HBsAg: Hepatits B surface antigen, HCC: hepatocellular carcinoma, n.s: not statistically significant

Table 2: The reported prevalence of anti-HCV positive status in non-cirrhotic and cirrhotic patients with hepatocellular carcinoma (HCC) in the literature.

Reference	Anti HCV antibody positive status		p-value
	Non-cirrhotic HCC patients (%)	Cirrhotic HCC patients (%)	
Trevisani et al[26]	15/28 (53.6%)	104/138 (75.4%)	0.03
Bralet et al[49]	2/80 (2.5%)	68/250 (27.0%)	0.0001
Shimada et al[29]	22/42 (52.4%)	243/332 (73.2%)	0.007
Grazi et al[11]	33/135 (24.4%)	182/308 (59%)	<0.001
Chang et al[9]	39/216 (18.1%)	57/208 (27.4%)	0.02
Kumar et al[112]	1/52 (1.9%)	22/137 (16.1%)	n.s

HCV: Hepatitis C virus, HCC: hepatocellular carcinoma, n.s: not statistically significant

HBV can directly cause hepatic carcinogenesis, independent of the development of cirrhosis.[30] This is possible because HBV is a DNA virus and hence can integrate into host DNA leading to host DNA microdeletions and produce HBx protein that modifies the host growth control genes.[18]More recently, many studies have shown that the mutations in basal core promoter region, HBeAg seropositivity, HBV genotype C and a high viral load (10^{4-5}copies/ml) are independent predictors of HCC development even in the absence of cirrhosis.[31-33] Hence in the future, identification of these factors could be applied to predict HCC risk in HBs Ag carriers irrespective of the presence of cirrhosis.[24]

The main mechanism of HCC development in chronic HCV infection is due to sustained viral replication leading to necro-inflammatory process. This results in high proliferative rate and increased risk for DNA mutation. Accumulation of these genetic changes over time confers a survival advantage with abnormal phenotype. Hence, nearly all HCV related HCC occurs against a background of advanced liver fibrosis or cirrhosis.[5,34,35] However, specific HCV gene products (core, NS3, NS4B and NS5A)[36,37] has produced malignant transformation in murine fibroblast culture suggesting that HCV also has a direct carcinogenic potential.[38,39,40]

The detection of HBV and HCV infections by serology underestimates their etiological role because HBV-DNA and HCV-RNA fragments have been identified in livertissue and/or serum of 18% to 33% of patients respectively, in non-cirrhotic HCC individuals with negative serological markers.[41]

2. Alcohol intake:

Numerous studies have addressed that fact that heavy alcohol intake has been less common in non-cirrhotic HCC patients (Table 3). This is in concordantwith the hypothesis that hepato-carcinogenic

potential of alcohol is almost always due to development of cirrhosis.[42.43]

Table 3: The reported prevalence of alcohol intake in non-cirrhotic and cirrhotic patients with hepatocellular carcinoma (HCC) in the literature.

Reference	Alcohol intake		
	Non-cirrhotic HCC patients (%)	Cirrhotic HCC patients (%)	p-value
Trevisani et al[26]	15/91 (16.5%)	105/350 (30.0%)	0.01
Nzeako et al[27]	25/342 (7.3%)	130/462 (28.1%)	<0.0001
Bralet et al[49]	11/80 (13.7%)	73/250 (29.2%)	0.009
Shimada et al[29]	44/63 (69.8%)	232/433 (53.6%)	0.022
Grazi et al[11]	29/135 (21.5%)	67/308 (21.7%)	n.s
Chang et al[9]	98/223 (43.9)	99/222 (44.6%)	n.s
Kumar et al[112]	5/52 (9.6%)	25/137 (18.2%)	n.s

HCC: hepatocellular carcinoma, n.s: not statistically significant

3. Toxic substances:

Non-cirrhotic HCC can also occur due to the exposure of following genotoxic agents:

i. Aflatoxin B1, a toxin produced by the fungus Aspergillus flavus can contaminate many food products, such as cereals, nuts, spices, figs and dried fruit. This contamination is common in developing countries like India and other parts of Asia and Africa with a high HCC incidence.[44]A study by Qian et al[45] has linked the association the urinary excretion of

aflatoxin metabolites with a 4-fold increase in HCC risk. Infact, HBV infection increases the HCC risk in aflatoxinexposure to 60-fold when compared to the general population. Ming et al[46] has shown that HBV infection sensitizes hepatocytes to the aflatoxin-induced 249ser-p53 mutation.

ii. Industrial carcinogens (such as azo-dyes, organic solvents, vinyl chloride, pesticides, nitrosamines, arsenic, aromatic amines) and substances derived from tobacco (benzopyrene) have been shown to havehepato-carcinogenic potential in animal studies. Hence, these substances could also play a role in human carcinogenesis.

iii. Thorotrast (Radioactive elements) may also cause HCC, albeit much less frequently than angiosarcoma and cholangiocarcinoma.[47]

iv. Finally, tissue iron overload may act as a co-carcinogen factor, as suggested by the frequent observation of mild parenchymal iron excess in the non-tumorous liver tissue of most patients with non-cirrhotic HCC.[48,49,50]

4. Inherited diseases:

The development of non-cirrhotic HCC may also be attributed to rare inherited disorders such as:

i. Metabolic diseases such as hereditary hemochromatosis, alpha-1-antitrypsin (AT) deficiency, porphyria, hyper-citrullinemia and type I glycogen storage diseases.[24,51]

ii. Congenital diseases like congenital hepatic fibrosis and Alagille's syndrome.

iii. Hepatic vascular abnormalities, which are associated with inherited coagulation disorders such as Budd-Chiari syndrome, hepato-portal sclerosis and nodular regenerative hyperplasia.[24]

5. Steroid hormones:

Many case reports have described the development of HCC in non-cirrhotic patients with anabolic steroids taken for therapeutic purpose.[52,53] Although many studies have reported an higher risk for HCC in patients taking oestrogen for 8 years or more, a direct etiological role of contraceptive steroids is not yet established.[54,55] Forman et al[54] have demonstrated that oestrogen acts as initators or

promotors of carcinogenesis and also produce cellular and vascular changes thus amplifying an already developing tumor.

6. **Genetic mutations:**

Zuckmann-Rossi et al[56] postulated that the monoclonal mutations of both oncogenes and anti-oncogenes in hepatocellular adenoma are associated with the malignant transformation. Particularly, the gain of function mutation of β-catenin, which is found in 15-20% of hepatocellular adenomas are most likely to be associated with malignant transformation.[57]

Familial clustering of HCC has also been reported and a recent study by Hassan et al[58] has demonstrated that family history of liver cancer significantly increases the HCC risk irrespective of the HBV and HCV status. But, this study does not analyze separately for non-cirrhotic patients. However, it can be assumed that the possible relationship between a positive family history and HCC risk is the end result of environmental, genetic, behavioural and clinical risk factors.[58]

The molecular mechanisms of carcinogenesis involved in non-cirrhotic liver are beginning to be explored. Recently, Chaubertet al[59] reported a germ line mutation in tumor suppressor gene, $p10^{INK4}$ (MTSI) gene in 23% of European patients with non-cirrhotic liver and in 8% of

cirrhotic HCC patients. Although these studies support the existence of familial form of carcinogenesis, the confirmation of hereditary component in HCC risk awaits further studies of familial clusters.

HEPATO-CARCINOGENETIC PATHWAY:

Different authors have postulated different hepato-carcinogenetic pathway in non-cirrhotic HCC. This hypothesis is based on different scenario of genetic alteration found in non-cirrhotic HCC, that is, a tendency towards a low incidence of p53 mutation and a high rate of β-catenin mutation, p14 inactivation and global gene methylation in non-cirrhotic HCC.[60]

Two recent studies by Chiappiniet al[61] and Togni et al[62] have found the presence of microsatellite instability (MSI), a sign of defect in DNA mismatch repair, in non-cirrhotic HCC patients with non-alcoholic and non-virally infected livers.

PATHOLOGY:

The non-tumor bearing portion of liver in patients with non-cirrhotic HCC usually show steatosis, steato-hepatitis, varying degree of fibrosis, iron excess or other metabolic disorder and hence only few cases show a normal parenchyma.[25,26,29] In addition, large cell dysplasia

is seen in 25-40% of cases.[25,63] This figure reduces to 6-20% in patients with non-fibrotic liver.[29,49]

Most (50-85%) non-cirrhotic patients with HCC present as a large, solitary mass (about 10cm in most series).[26, 64-67]Multinodularity is not as common (18% vs. 34%) as seen in cirrhotic HCC[26]. This is possibly due to both the delay in presentation and distinct mechanism of hepato-carcinogenesis in non-cirrhotic HCC.

According to World Health Organization (WHO) histological classification, the trabecular type is the most common type (40-75%) in both non-cirrhotic HCC, and cirrhotic HCC.[25-27,49,56] The scirrhous type and mixed hepatocellular/cholangiocellular carcinoma tend to occur more commonly in a non-cirrhotic background[68,69], whereas Fibrolamellar HCC is almost exclusively limited to non-cirrhotic liver (115 vs. 1.5%).[27]

Two larger studies by Nzeakoet al[27] and Shimada et al[29] have shown that encapsulation is more common in non-cirrhotic HCC, however, this finding has not been confirmed in other studies.

A recent series by Trevisaniet al[26] have demonstrated that the extra-capsular extension of HCC (invasion of surrounding structure

and/or metastases) is more common in non-cirrhotic HCC when compared to cirrhotic HCC.

Although the more advanced stage of tumor at presentation in non-cirrhotic patients can be attributed to delayed diagnosis, a greater biological aggressiveness cannot be excluded, because some authors have reported poor tumor differentiation and early portal vein invasion in non-cirrhotic HCC.[11,29] At present, the available data on this issue is controversial, as other authors have reported opposite results.[9,26,27]

DIAGNOSIS:

According to the current international guidelines for the management of HCC, routine ultrasonographic surveillance is now being performed in all patients with chronic liver disease. This has resulted in early detection of tumor, usually before the manifestation of clinical symptoms. In contrast, in otherwise healthy person or with undiagnosed liver disease, HCC are generally detected late, usually after the appearance of symptoms such as abdominal pain or discomfort in right upper quadrant, jaundice or toxic syndrome (anorexia, weight loss, malaise, asthenia, fever).[35] Trevisani et al[26] have reported that non cirrhotic patients with HCC has a symptomatic presentation in about 80% with the remaining being detected incidentally. This finding

suggests that the delay in presentation and diagnosis accounts for most differences in pathological differences between non-cirrhotic and cirrhotic patients.

Most studies have demonstrated that the serum α-fetoprotein (AFP) level rarely exceeds 40ng/dl in non-cirrhotic when compared to cirrhotic patients with HCC (30-67% vs. 60-85%).[26,27,64,65] This suggests the likely role of cirrhosis as independent promoter of moderate AFP elevation. However, the prevalence of level of AFP considered "diagnostic" for HCC is similar in both the groups.[26,64]

PREOPERATIVE EVALUATION:

The preoperative investigations for HCC should focus on three main issues:

1. Tumor status
2. Underlying liver status
3. Patient performance status.

1. Tumor status:

Assessment of tumor extent is best achieved with cross sectional imaging such as dynamic contrast enhanced Magnetic resonance imaging (MRI) and/or 4-phase multi-detector Computerized tomography

(Figure: 10-12). There are no data at present to support the value of PET scanning in HCC. A chest X-ray, CT chest and Bone scan are recommended to rule out extra-hepatic disease. Many studies have shown that the most common sites of metastatic spread of HCC are lung, bone, peritoneum and adrenals. Although these sites of spread may be detected by standard imaging techniques, peritoneal disease requires staging laparoscopy.

2. Underlying liver status:

Blumgart et al[18] have demonstrated that a healthy, non-cirrhotic liver may tolerate a resection of up to 80% due to the enormous regenerative capacity of liver. However, such favorable responses cannot be taken up for granted for extended hepatic resections. The risk of clinically significant liver insufficiency can be avoided only if there is 50% reduction in functioning liver parenchyma even in non-cirrhotic liver. Although helpful, the Child-Pugh score and Model for end-stage liver (MELD) score are not adequate to select patients for major hepatic resection.

Most centers in Asia perform indocyanine green clearance (ICG-15) at 15 minutes as defining criterion for selection of liver resection. Another important indicator of post-operative liver

insufficiency is the pre-operative evaluation of the post-operative future liver remnant (FLR). CT is used to assess the ratio of future remnant (FLR) and total liver volume (TLV). The consensus panel recommends that this ratio should be at least 30-40% in non-cirrhotic patients. In patients with estimated FLR/TLV below the recommended values, pre-operative portal vein embolization (PVE) should be considered.

ROLE OF PRE-OPERATIVE PORTAL VEIN EMBOLIZATION (PVE):

PVE produces atrophy in portion of liver to be resected and compensatory hypertrophy in the portion of liver to be preserved. By reducing the risk of liver failure, complication rate and hospital stay, PVE increases the safety of resection and expand the indication for liver resection in otherwise poor candidates for hepatectomy.[18]

A recent meta-analysis by Abulkhiret al[70] have reviewed 37 published series of preoperative PVE in 1088 patients (265 patients with HCC, the reminder with cholangiocarcinoma or liver metastases). In 2-4 weeks, there was significant hypertrophy of FLR that was independent of technique and 85% of patients underwent planned liver resection. The reasons for not operating in remaining 15% of patients were inadequate hypertrophy (n=18), tumor progression (n=43), extra-hepatic spread

(n=35) and other reasons such as refusal for surgery, poor medical condition, altered treatment approach for variety of reasons (n=35). In patients who underwent laparotomy, 27 patients were found unresectable, mainly due to advanced or unresectable disease. Of the remaining patients who underwent liver resection, transient liver failure was seen in only 2.5% (n=23), and death due to acute liver insufficiency in 0.8% (n=7).

ROLE OF PRE-OPERATIVE TACE:

The role of TACE in pre-operative setting remains conflicting. In a RCT by Wu et al, there was no significant difference in overall survival or disease free survival. In addition, they have reported higher incidence of extra-hepatic recurrence with pre-operative TACE possibly due to easier tumor cell dislodgement during surgery.[71]

Similarly, Shimada et al[72] have found pre-operative TACE to be a poor prognostic factor in univariate analysis, but not in multivariate analysis. The potential disadvantages of pre-operative TACE are impairment of pre-operative liver function, delayed in planned surgery and difficult surgery due to development of collateral vessels and severe inflammatory changes around tumor. At present, there is no sufficient data to support pre-operative TACE in HCC.

STAGING:

Numerous staging systems have been proposed for clinical classification of HCC. The standard classification in any cancer is based on TNM staging, however in HCC, the 7th TNM classification has several limitations.[73] First, microvascular invasion is assessed by pathology, hence only available in patients (~ 20%) undergoing surgery. Second, it does not include information regarding liver function status or patient performance status. The more popular Child-Pugh classification and Okuda staging serve only to class prediction in HCC patients. The five more comprehensive staging that have been broadly tested are: 3 European [the Barcelona Clinic Liver cancer (BCLC)[74] staging, the cancer of liver Italian program (CLIP) [75]classification, the French classification[76]] and 2 Asian [the Chinese University Prognostic Index (CUPI)[77] score and the Japan Integrated staging with biomarkers (bm-JIS)[78]]. Overall, the most external validated staging systems are BCLC, CUPI, CLIP and bm-JIS with only two include prognostic variables (BCLC and CUPI) and only one (BCLC) assign treatment allocation to specific prognostic subgroups. Hence the current EASL-EORTC guidelines recommend BCLC for staging HCC.[79]

TREATMENT AND SURVIVAL:

The various treatment options for non-cirrhotic patients with HCC are:

1. Hepatic resection
2. Liver transplantation
3. Trans-arterial embolization
4. Radio-embolization
5. Radio-frequency ablation
6. Systemic chemotherapy

1. HEPATIC RESECTION:

Regardless of etiology, the optimal management in HCC is complete resection of tumor. Numerous studies have shown that the patients with non-cirrhotic HCC undergo resection more than the reported (12-28%) incidence in patients with underlying cirrhosis.[80,81] In spite of large tumor size, the preserved liver function in non-cirrhotic patients allows major hepatic resections to be performed quite safely. In fact, despite major hepatic resection, the post-operative morbidity and mortality are rather low in these patients.[7,11,66,67,82]Moreover, the overall survival and recurrence free survival are better in non-cirrhotic patients with HCC than in patients with cirrhosis.[9,11,29,83,84]

The overall survival and disease-free survival of patients resected for non-cirrhotic HCC are depicted in Table16. The 5-year overall survival rate ranges between 25% and 81% with best figures reported in in non-cirrhotic HCC. Similarly, the 5-year disease-free survival ranged from 24% to 58% with best value achieved in non-cirrhotic patients.[82]

The independent factor for overall survival in patients with non-cirrhotic HCC is the rate of tumor recurrence, which varies between 27% and 73% in different series, as outlined in table-16.[82] Most (2 out of 3) recurrences occur in the initial two post-operative years, but can be delayed to 10 years or more. Up to 40% recurrences are amenable to second hepatectomy, but long-term survivals are noted in patients with early recurrence. These results highlight the importance of follow-up during the first two post-operative years and the need for prolonged surveillance for aggressive management of recurrences.[7,10,65,67,82,83,85]

2. LIVER TRANSPLANTATION:

The role of orthotopic liver transplantation (OLT) in treatment of patients with non-cirrhotic HCC is a subject of controversy. A systematic review conducted by Houbenet al[6] included all published series of OLT for non-cirrhotic HCC performed between 1966 and 1998 has shown that the long-term survival in these patients is poor with 5-

year survival rate of 11%. This dismal figure suggest the advanced tumor stage at the time of OLT, which resulted in recurrences in about 50% of patients, mostly (>75%) in the first 2 years, indicating the likely possibility of extra-hepatic micrometastases.[6]

The specific selection criteria for transplantation in non-cirrhotic HCC are lacking. The commonly adopted criteria in non-cirrhotic HCC patients are actually proposed for cirrhotic patients, which is inappropriate because most non-cirrhotic HCC are outside the Milan criteria at the time of diagnosis and those fulfilling these criteria are potentially resectable tumors. In addition, the tendency towards OLT in non-cirrhotic HCC is limited by the report that the outcome after resection in non-cirrhotic HCC within Milan criteria is comparable to that expected in cirrhotic patients transplanted within Milan criteria. Pragmatically, OLT could be reserved as a salvage treatment for non-cirrhotic patients with post-resection tumor recurrence and those with high risk of post-hepatectomy liver failure.[9,85]

3. TRANS-ARTERIAL EMBOLIZATION:

The basic physiological principle that makes TAE feasible is that most of blood supply (90% to 100%) to liver tumors is derived from the hepatic artery, thus embolization of tumor-feeding arteries leads to

selective ischemic damage of the tumor, while sparing the normal liver parenchyma supplied mainly by the portal vein. Moreover the pharmacokinetic advantage of selective loco-regional drug administration further enhances the theoretic benefit.

Basically there are three types of trans-arterial therapy:

1. Trans-arterial embolization (TAE) with bland particles.
2. Trans-arterial chemo-embolization (TACE) with or without lipiodol.
3. Trans-arterial chemotherapy (TAC) alone or with lipiolol.

A meta-analysis by Camma et al[86] have failed to demonstrate any significant survival differences between TAE and TACE, in spite of a trend towards longer survival with TACE.

Indications for TACE:

1. Unresectable large hypervascular liver tumor.
2. Intermediate BCLC stage HCC (Okuda staging 1 to 2, Performance score 0 and large or multinodular HCC)
3. Spontaneous rupture of HCC

4. As neoadjuvant therapy to downsize tumor before resection or bridging therapy in patients awaiting liver transplantation.

Contraindication to TACE:

1. Extensive tumor involvement of more than 50% to 70% of liver and class C cirrhosis.
2. Main portal vein occlusion.
3. Active gastrointestinal bleeding, extra-hepatic spread, hepatic encephalopathy and biliary obstruction.
4. Anaphylactoid reaction to contrast agents, cardiac or renal insufficiency, uncorrectable coagulopathy and severe peripheral vascular disease.

The mean diameter of tumor treated by TACE was 5.2cm in randomized controlled study by Llovet et al[87] and 5cm in GETCH[88] (Grouped Etude et de Traitement du CarcinomeHepatocellulare) study. In addition to tumor size, factors such as good liver function, performance status – 2, Okuda stage II were associated with survival benefit. However, tumor size >5cm is a strong negative factor affecting survival after TACE.

The survival benefit from TACE was not demonstrated in 3 early randomized controlled trails (RCT) by Pelletier et al[89] (1990), Grouped Etude et de Traitement du Carcinome Hepatocellulare[88] (GETCH study-1995) and Camma et al[86] (2002). However, 2 newer RCT's from Barcelona (Llovetet al[87], 2002) and Hongkong (Lo et al[90], 2002) demonstrated significant survival advantage with TACE. A recent meta-analysis of all RCTs published from 1978 to 2002, American Association for study of liver diseases (AASLD-2005, Bruix and Sherman et al[35]) and European association for study of liver (EASL-2001, Bruix et al[5]) have recommended TACE as first line non-curative therapy for non-surgical patients with large or multifocal HCC without vascular invasion or extra-hepatic spread.

A recent advancement in TACE is the usage of drug eluting beads (DEBs) which slowly releases chemotherapeutic drug thereby reducing the systemic toxicity. Early results are promising but most series are associated with short-term follow-up only.[91]

4. RADIO EMBOLIZATION or SELECTIVE INTERNAL RADIATION THERAPY (SIRT):

Radio-embolization is a method of delivering localized radiation dose of up to 150 Gy to tumor thereby reducing the complication of

external radiation. ^{90}Yttrium is the most commonly used radioactive element for radio-embolization. It is a pure β-emitter with tissue penetration ranging from 2.5 to 11mm. Radio-embolization was first studied by Nolan and Grady[92] (1969) using ^{90}Yttrium oxide ($^{90}Y_2O_3$) contained in metal particle of 50-100 μm in size. Their study was limited by small number of patients but showed a favorable response with decrease in tumor size. The subsequent ^{90}Y study was published by Mantravadiet al[93] (1982) concluding that patients with hypervascular tumor are more likely to be benefit from radio-embolization. Based on animal safety studies, Shepherd et al[94] conducted phase I studies suing ^{90}Y glass microspheres and reported that doses of up to 150 Gy were tolerable with minimal toxicities. In view of the encouraging results, a phase II study performed by same authors showed a 20% response rate with doubling of survival duration (635 vs. 323 days) in patients who underwent radio-embolization.

Analysis from these studies and other trials have demonstrated that tumor-liver ratio <2, low Okuda stage, low AFP favored longer survival whereas elevated bilirubin was associated with post-treatment liver dysfunction.[95] The role of radio-embolization in HCC patients is evolving and further trials are needed to document their safety and clinical efficacy.

5. RADIOFREQUENCY ABLATION:

Radiofrequency ablation (RFA) destroy tumor by generating heat within a lesion. During RFA, a high frequency alternating current changes the direction of ions around an alternating electrode. This produces frictional heating of tissues and when tissue temperature increases above 60^0 C, loss of cellular structure and protein denaturation occurs, resulting in cell death. RFA can be performed by percutaneous, laparoscopic or open (laparotomy) approach.

Clinical trials of RFA for HCC have shown promising results andLivraghiet al[96] showed a local response rate of only 2.8% at a median follow-up of 31 months. Poon et al[97] demonstrated a complete response rate of 91% for large (>3cm) HCC and showed rate of local recurrence, distant recurrence were independent of tumor size. Two randomized control trials by Chen et al[98] and Lu et al[99] have demonstrated therapeutic equivalence of RFA, when compared with resection in small HCC, until more prospective studies have been performed, resection remains the initial choice in these patients.

6. SYSTEMIC CHEMOTHERAPY:

The role of systemic chemotherapy is very limited in patients with HCC. The response rate with single agents is about 10% to 15%.[100]

A recent retrospective study by Edelineet al[101] reported that combination chemotherapy with Epirubicin, cisplatin, and 5-flurouracil/ capecitabine was associated with objective response in 25% of cases with unresectable HCC.

Lau et al[102] have shown that 10% of advanced HCC patients underwent successful resection after tumor downsizing with combination chemotherapy composed of Cisplatin, interferon alfa, Adriamycin and 5-flurouracil (PIAF) regimen. The 3-year survival rate was 53% for those who underwent resection following PIAF regimen. In the multivariate analysis of 149 patients who received PIAF by the same author, non-cirrhotic patients with normal bilirubin level had a shown a better response to combination chemotherapy.

New molecular drug, Sorafenib which is an oral multi-kinase inhibitor that targets Raf kinase and receptor tyrosine kinase has shown promising results in phase III randomized placebo controlled (SHARP trial) trial[103] involving 602 patients with advanced HCC in terms of improved survival and median time to progression. This result has suggested sorafenib as first line therapy for patients with advanced HCC, although no patient is reported to have tumor downsized to undergo resection. Hence, the optimal management of patients with advanced and unresectable HCC is not yet established.

MATERIALS AND METHODS

MATERIALS AND METHODS

STUDY DESIGN:

Prospective study

STUDY PERIOD:

September 2010 to December 2012

INCLUSION CRITERIA:

All consecutive patients with histologically proven HCC in non-cirrhotic, non-fibrotic liver undergoing liver resection will be included in the study

EXCLUSION CRITERIA:

1. Patients undergoing liver resection with palliative intent were excluded from the study.
2. Histological proven HCC in cirrhotic or fibrotic background.
3. Patient refuses to give informed consent to be included in the study.

METHODOLOGY:

PATIENTS:

Between August 2010 and December 2012, 76 patients with HCC underwent liver resection in the Institute of Surgical gastroenterology and liver transplantation at Government Stanley Medical College and Hospital. Of the 76 patients who had liver resections for HCC, 30 patients had no underlying parenchymal liver disease (no cirrhosis or fibrosis) and these 30 patients were included in the study

PREOPERATIVE EVALUATION:

Routine pre-operative evaluation include recording of detailed demographic profile, history of presenting symptoms, physical examination and routine laboratory investigations like complete hemogram, renal function test with electrolytes, liver function test including albumin. Data regarding underlying liver disease (such as past or current hepatitis B virus or hepatitis C virus infection, alcoholic or non-alcoholic steatohepatitis, iron overload and hemochromatosis) and risk factors for the development of HCC such as chronic alcohol intake ($\geq$ 40 g/day), tobacco consumption ($\geq$ 20 pack years), diabetes mellitus, overweight or obesity(BMI > 25 kg/m^2), aflatoxin or carcinogenic

substance exposure) were also recorded. Serum alpha fetoprotein and upper gastro-intestinal endoscopy were done in all patients.

Pre-operative investigations performed to assess the extent of disease included Chest X-ray, abdominal ultrasonography, contrast enhanced computerized tomography (CT) and/or MRI in all patients and CECT thorax in selected patients. The diagnosis of HCC was based on either pre-operative imaging and serum AFP level or rarely biopsy. Liver function status was assessed by the Child-Pugh grading. Patient performance status at the time of diagnosis was determined according to the Eastern Co-operative Oncology Group (ECOG).

SURGERY:

Prior to surgery, all patients were discussed in a multidisciplinary meeting in order to ensure an optimal management strategy. Staging laparoscopy was done immediately before surgery in all patients. In addition to evaluation of peritoneal deposits, staging laparoscopy allowed assessment of future liver remnant size and severity of cirrhosis, when major liver resection was planned.

The operation was performed through a Maakuchi's incision or bilateral subcostal incision with an upward midline extension (Mercedez-Benz incision). Intra-operative ultrasound was done in all

cases to detect any additional tumor and relationship of tumor to vasculo-biliary structures. Selective vascular inflow and outflow control was obtained followed by parenchymal transection under low central venous pressure (CVP) anaesthesia, using a combination of kellyclasia, harmonic, ultrasonic dissector and water jet.

Anatomic resections were defined according to the Brisbane terminology described by International Hepato-Pancreatico-Biliary Association (IHPBA) and Non-anatomical resections were defined as atypical or wedge resection with tumor free margin of at least 1cm. A major hepatic resection was defined as resection of 3 or more segments of liver according to Couinaud's classification of liver segments and minor hepatic resection was defined as resection of 2 or less segments of liver.

Intra-operative parameters like type of liver resection (Major/minor, anatomic/non-anatomic), duration of surgery, blood loss, number of blood transfusion and intra-operative complications were recorded. All patients received prophylactic broad-spectrum antibiotics.

POST-OPERATIVE CARE:

All patients were monitored in the intensive care unit during the initial post-operative period. Careful attention was paid to hydration,

oxygenation and tissue perfusion. Intravenous albumin and diuretics were administered in selected patients to reduce ascites. Early ambulation was encouraged and oral intake was resumed once the bowel activity was restored. Liver function test with prothrombin time and INR were routinely done in 1^{st}, 3^{rd} and 5^{th} post-operative days to detect post-operative liver insufficiency. All post-operative complications were recorded and were classified as: Infectious (Anastomotic leak, Intra-abdominal abscess, Wound infection, Pneumonia, Septicemia) and Non-infectious (Pulmonary embolism, Renal failure, Cardiac events including Acute coronary syndrome and Acute MI). Length of hospital as well as post-operative stay were recorded.

HISTOPATHOLOGY:

All the resected specimens were analyzed by the experienced pathologists. A standard histo-pathological assessment of tumoral and non-tumoral tissue was performed.

The macroscopic features of tumor such as size, number, tumor capsule and vascular invasion were recorded. Tumors were classified using World Health Organization criteria (such as trabecular, pseudoglandular, compact, scirrhous or mixed) and graded using Edmondson and Steiner classification into well-differentiated (grade I),

moderately-differentiated (grade II) and poorly differentiated (grade III). A clear resection (R0) margin was defined as negative of 1mm from the inked margin or 1mm of liver tissue between capsule and margin. Macroscopic vascular invasion was defined as presence of tumor thrombi in right or left main branches of the hepatic veins or the portal veins. Microscopic vascular invasion was defined as presence of tumor emboli within central vein, capsular vessels or portal vein and hepatic vein radicles.

Non-tumoral tissue was assessed in area distant to tumor to avoid inflammatory or fibrotic changes caused by tumor itself. Fibrosis and chronic activity were graded using the METAVIR grading system. Steatosis was graded according to the percentage of steatotic hepatocytes into mild (5% to 20%), moderate (20% to 50%) and severe (>50%). Iron overload was graded according to Modified Searle scale into mild or grade I (iron barely visible at low magnification but confirmed at high magnification, moderate or grade II (iron visible at low magnification and only in zone 1, and severe or grade III (iron visible at low magnification occupying most of acinus). Precancerous lesions in the non-tumoral liver were defines by the presence of liver cell dysplasia, clear cell foci or iron-free foci in otherwise iron-overloaded liver.

FOLLOW UP:

All patients were followed up in the out-patient department, every month during the first 3 months, then every 3 months for initial 2 years and every 6months thereafter. In each visit, physical examination, liver function test, serum AFP and abdominal ultrasound was performed. CT scan was performed at month 6 and then every year.

The diagnosis of recurrence was based on clinical, laboratory (elevated serum AFP level) and radiological (abdominal ultrasound/CT, chest X-ray) findings. The number and pattern of recurrence (intrahepatic, extra-hepatic or both) were also recorded. Patients with isolated and resectable intra-hepatic recurrence underwent re-resection. All others were treated with TACE, systemic therapy or best supportive care.

The follow up period of this study was closed in February 2013 to ensure that every patient had at least 2 months of observation following surgery. The above described protocol was approved by our institutional ethical committee.

STATISTICAL ANALYSIS:

All clinico-pathological and follow-up data were prospectively collected and entered with regular update of any tumor recurrence for each patient after each follow-up. Categorical variables were expressed as percentages and compared using chi-square test or Fisher exact test. Continuous variables were expressed as mean ± SD and compared using the student-t test. Survival and recurrence were expressed as median ± SEM. Patient survival and recurrence were calculated using the Kaplan-Meier test and compared using the log-rank test. Clinico-pathological variables found to bear prognostic significance in univariate analysis were entered into Cox multivariate proportional hazard model to determine which of these factors possessed independent predictive value. p-value< 0.05 was considered statistically significant and analysis was carried out using the Statistical Package for the Social Sciences (SPSS 18.0; SPSS, Inc., Chicago, IL, USA)

RESULTS

RESULTS

This prospective study was conducted in the Institute of Surgical gastroenterology and liver transplantation, Government Stanley Medical College and Hospital from August 2010 to December 2012. During the study period, a total of 76 patients underwent liver resection for hepatocellular carcinoma. Of the 76 patients who had liver resections for HCC, 30 patients (39.47%) had no underlying parenchymal disease (no cirrhosis or fibrosis) and were included in the study.

The clinical characteristics of 30 patients with non-cirrhotic HCC are shown in table-4. The mean age at presentation was 48.23 years (range: 13-77). The age distribution (Figure 2) of 30 patients shows that the majority of patients (67%) are in the fifth and sixth decades. The gender distribution (Figure 3) shows that there were 19 males (63%) and 11 females (37%) with male: female ratio of 1.7: 1.

Table 4: Clinical characteristics of 30 patients with HCC in non-cirrhotic liver studied.

Variables	**n**	**%**
Age		
<50 years	13	43
>50 years	17	57
Sex		
Male	19	63
Female	11	37

Risk factor		
Hepatitis B virus infection	4	13
Hepatitis C virus infection	0	0
Chronic alcohol intake	9	30
Tobacco smoking	9	30
Diabetes mellitus	8	26.7
Obesity	3	10
Unknown	12	40
Symptoms		
Abdominal pain	30	100
Weight loss and anorexia	28	93
Abdominal mass	7	23
Fever	4	13
Jaundice	2	6
Hepatomegaly	17	57
ECOG performance status		
0	26	87
1	3	10
2	1	3
Pre-operative biopsy		
Present	3	10
Absent	27	90

ECOG: Eastern Co-operative Oncology Group.

The potential risk factors for the development of HCC were present in 18 patients (60%). Four patients (13%) presented with current or past hepatitis B viral infection and no patient was positive for anti-HCV antibody. Tobacco and alcohol consumption were found in 9 patients (30%). Diabetes mellitus was observed in 8 patients (26.7%)

and overweight in 3 patients (10%). In contrast, 12 patients (40%) did not reveal any underlying risk factor for the development of HCC.

Abdominal pain was the most common presentation in the non-cirrhotic HCC patients, which was noted in all 30 patients (100%), followed by anorexia and weight loss in 28 patients (93%), abdominal mass in 7 patients (23%), fever in 4 patients (13%) and jaundice in 2 patients (6%). None of the patient was asymptomatic at the time of presentation. Hepatomegaly was observed in 17 patients (57%) and none of the patients had ascites. Three patients had undergone pre-operative biopsy and none of the patient received any type of pre-operative treatment.

The pre-operative laboratory investigations done in 30 patients with non-cirrhotic HCC were listed in table-5. The mean hemoglobin level was 10.7 g/dl ± 1.6 (range: 8.5-14). Serum bilirubin was elevated in 2 patients (6%). The mean serum bilirubin value was 1.1 mg/dl ± 0.83 (range: 0.25-3.6). Serum aspartate transaminase (AST) was elevated in 19 patients (63%) with mean value of 84.6 U/L ±91.45 (range: 21-498). Serum albumin was low in 17 patients (57%) with mean value of 3.42 g/d ± 0.55 (range: 2.5-4.9). Serum alpha-fetoprotein level was normal in 20 patients (67%) and elevated above 1000ng/ml in only 2 patients (6%). The mean AFP level was 6.8 ng/ml ± 5922.9 (range: 0.3-32476).

Table 5: Pre-operative laboratory data in 30 patients with HCC in non-cirrhotic liver studied.

Laboratory parameter (unit)	Normal range	Mean ± Standard deviation (range)
Hemoglobin (gm/dl)	14-18	10.73 ± 1.6 (8.5-14)
Total leucocyte count (cells/cu.mm)	4000-11000	8346.3 ± 2428 (2200-15000)
NLR	1-8 x 10^9/L	2.77 ± 1.58 (1.09-7.33)
ESR (mm/hr)	0-20	41.6 ± 26.49 (8-120)
Platelet (cells/cu.mm)	1.5 -4	3.71 ± 1.80 (1.42-7)
Prothrombin Index	70-100%	97.36 ± 5.66 (77.77-100)
INR	0.8-1.2	1.04 ± 0.09 (1-1.4)
Sugar (mg/dl)	<160	120.93 ± 48.85 (67-268)
Urea (mg/dl)	10-50	21.67 ± 7.70 (13-50)
Creatinine (mg/dl)	0.6-1.1	0.80 ± 0.24 (0.4-1.54)
Bilirubin (mg/dl)	0-1	1.12 ± 0.83 (0.25-3.6)
AST (U/L)	0-40	84.6 ± 91.45 (21-498)
ALT (U/L)	0-37	47.66 ± 35.70 (8-173)
GGT (U/L)	0-45	98.93 ± 196.27 (10-1050)
SAP U/L)	0-290	261.87 ± 123.56 (85-617)
Albumin (g/dl)	3.8-4.4	3.42 ± 0.55 (2.5-4.9)
AFP (ng/ml)	<20	6.8 ± 5922.9 (0.3-32476)

NLR: Neutrophil-leucocyte ratio, ESR: Erythrocte Sedimentation rate, INR: Internationalized normalized ratio, AST: Aspartate transaminase, ALT: Alanine transaminase, GGT: Gamma-glutaryltransferase, SAP: serum alkaline phosphatase, AFP: Alpha feto-protein.

The extent and type of resection performed were outlined in table-6. Out of 30 patients, 25 patients (83%) underwent major hepatectomy whereas only 5 patients (17%) underwent minor hepatectomy (Figure 4). The most common procedure performed was right hepatectomy (Figure: 13-16), which was done in 12 patients (40%), followed by left hepatectomy in 6 patients (20%), extended right hepatectomy in 5

patients (17%), bi-segmentectomy in 2 patients (6.7%) and extended left hepatectomy, central hepatectomy, left lateral segmentectomy (Figure 17 and 18) in 1 patient (3.3%) each. Non-anatomical resection was done in 2 patients (6.7%). Three patients (10%) underwent enbloc resection of adjacent organ (diaphragm) involvement to achieve R0 resection.

Table 6: Type and extent of liver resection in 30 patients with HCC in non-cirrhotic liver studied.

Surgical procedures	**n**	**%**
Major Hepatectomy (n=25)		
Right Hepatectomy	12	40
Left Hepatectomy	6	20
Extended Right Hepatectomy	5	16.7
Extended Left Hepatectomy	1	3.3
Central hepatectomy	1	3.3
Minor Hepatectomy: (n=5)		
Left lateral segmentectomy	1	3.3
Bisegmentectomy	2	6.7
Non-anatomical resection	2	6.7

The mean duration of operation was 2.45 ± 0.59 hours (Table-7). The mean blood loss during surgery was 216.5 ± 119.32 ml (range: 100-720ml). There was a need for blood transfusion in 2 patients (6.7%).

Table 7: Perioperative factors in 30 patients with HCC in non-cirrhotic liver studied.

Peri-operative factors	**Mean ± Standard deviation or n (%)**
Operative time (hours)	2.45 ± 0.59
Blood loss (ml)	216.5 ± 119.32
Need for blood transfusion	2 (6.7%)
Mean post-operative stay (days)	16.7 ± 7.0
Morbidity	15 (50%)
Mortality	1 (3.4%)

The mean post-operative length of stay was 16.7 ± 7.0 days. (range: 9-35 days). In-hospital mortality was noted in 1 patient (3.4%) due to post-operative liver failure.

The data regarding the post-operative complication was summarized in table-8. Overall, the post-operative complications occurred in 15 patients (50%). The most common post-operative complication (Figure 5) was intra-abdominal collection and wound infection noted in 6 patients (20%) each, followed by sepsis in 5 patients (16.7%), Post-operative liver failure and chest infection in 4 patients (13.4%) each. Bile leak was noted in 3 patients (10%) and renal failure in 1 patient (3.4%).

Table 8: Overall postoperative complications occurred in 15 of 30 patients with HCC in non-cirrhotic liver studied.

Post-operative complications	**n**	**%**	**Death (3.4%)**
Intra-abdominal collection	6	20	
Post-operative liver failure	4	13.4	1
Renal failure	1	3.4	
Chest infection	4	13.4	
Wound infection	6	20	
Bile leak	3	10	
Sepsis	5	16.7	

The mean size of tumor on histo-pathological examination was 13.2 ± 5.22 cm (range: 5-25cm). The majority of patients (76.7%) had solitary tumor (Table-9). Tumor encapsulation was noted in 19 patients

(63.3%) with capsular invasion of tumor observed in 5 patients (26.3%). Histological differentiation of tumor was grade I in 13 patients (43.3%), grade II in 8 patients (26.7%) and grade III in 9 patients (30%). Microvascular invasion was observed in 15 patients (50%) but none of the patient had macrovascular invasion. The resected margin was found positive for tumor cells in 8 patients (26.7). The surrounding non-tumor liver showed steatotic changes in 4 patients (13.3%).

Table 9: Histo-pathologic characteristics of tumor and surrounding parenchyma in 30 patients with HCC in non-cirrhotic liver studied.

Variables	n	%
Size		
<6cm	5	16.7
>6cm	25	83.3
Number of tumor		
Solitary	23	76.7
Multiple	7	23.3
Encapsulation		
Present	19	63.3
Absent	11	36.7
Differentiation		
I	13	43.3
II	8	26.7
III	9	30.0
Microvascular invasion		
Present	15	50.0
Absent	15	50.0
Macrovascular invasion		
Present	0	0.0
Absent	30	100
Capsular invasion		
Present	5	26.3
Absent	14	73.7

Margin		
Positive	8	26.7
Negative	22	73.3
Steatosis		
Present	4	13.3
Absent	26	86.7
pTNM-(AJCC-7th edition)		
I	6	21
II	14	45
III	9	29
IV	1	5
Okuda stage		
I	9	30
II	20	67
III	1	3

pTNM: pathologic tumor-node-metastasis

The follow-up rate was 100% with median follow-up of 405 days (range: 62-921 days). In the whole study population, tumor recurrence was identified in 14 patients (46.6%) within the follow-up period(Table-10). Of these 14 patients, 5 patients (35.7%) had isolated intra-hepatic recurrence, 3 patients (21.4%) had isolated extra-hepatic recurrence and 6 patients (42.8) had both intra-hepatic and extra-hepatic recurrence. Of the 5 patients with isolated intra-hepatic recurrence, 2 patients underwent re-resection, 2 patients received systemic chemotherapy and 1 patient was managed with supportive care. Two patients with isolated extra-hepatic recurrence and 2 patients with both intra and extra-hepatic recurrence were treated with systemic chemotherapy. The remaining 1

patient with isolated extra-hepatic recurrence and 4 patients with multiple recurrences were managed symptomatically.

Table 10: Pattern of recurrence and its management in 14 of 30 patients with HCC in non-cirrhotic liver studied.

PATTERN OF RECURRENCE (n=14)	**n**	**%**
Isolated Intra-hepatic recurrence		
Unifocal	3	21.4
Multifocal	2	14.2
Isolated Extra-hepatic recurrence		
Lung	2	14.2
Bone	1	7.1
Both Intra-hepatic and Extra-hepatic		
Unifocal intra-hepatic + Extrahepatic	2	14.2
Multifocal intra-hepatic + Extrahepatic	4	28.6
MANAGEMENT OF RECURRENCE		
Intra-hepatic alone		
Re-resection	2	
Systemic chemotherapy	2	
Best supportive care	1	
Extra-hepatic alone		
Systemic chemotherapy	2	
Best supportive care	1	
Both Intra-hepatic and Extra-hepatic		
Systemic chemotherapy	2	
Best supportive care	4	

OVERALL SURVIVAL:

At the time of analysis, there had been 11 deaths (36.7%) with 19 survivors (63.3%). The overall 1-, 2-, 3- year survival rates for the entire

study group are 86.7%, 66.7% and 63.3% respectively. At the end of 1, 2, 3 year, there were 26, 20, 19 alive patients respectively.

PROGNOSTIC FACTORS FOR OVERALL SURVIVAL:

Patient who died after operation were excluded from the analysis of prognostic factors for overall survival after liver resection for HCC in non-cirrhotic patients. In the univariate analysis, high grade tumor ($p = 0.007$), prothrombin time($p = 0.046$) and serum bilirubin level ($p = 0.034$) were significant predictors of poor long term survival (Table-11). In the multivariate analysis, only high grade tumor ($p = 0.039$) was identified as independent prognostic factor (Figure 6) for overall survival after liver resection for HCC in non-cirrhotic patients (Table-12).

Table 11: Clinico-pathological and operative prognostic factors for overall and disease-free survival in 30 non-cirrhotic HC patients (Univariate Analysis)

Characteristics	OVERALL SURVIVAL			DISEASE-FREE SURVIVAL		
	n	%	p-value	n	%	p-value
Age (yrs)			0.458			0.625
<60	11	18 ± 2.6		14	22 ± 1.9	
>60	19	29 ± 2.23		16	33 ± 2.21	
Gender			0.223			0.097
Male	12	11 ± 2.5		11	19 ± 2.7	
Female	18	28 ± 2.75		19	26 ± 3.9	
HBs antigen			0.792			0.511
Positive	4	25 ± 4.6		3	13 ± 7.1	
Negative	26	33 ± 1.9		27	27 ± 3.8	
Alcohol intake			0.091			0.351
Yes	4	31 ± 3.9		7	16 ± 4.6	
No	26	39 ± 4.1		23	21 ± 2.9	

AFP (ng/ml)			0.191			0.055
<20	9	39 ± 2.3		17	26 ± 4.59	
>20	21	27 ± 1.9		13	30 ± 2.77	
Bilirubin (mg/dl)			**0.034***			**0.012***
<1.5	3	23 ± 7.3		3	18 ± 6.53	
>1.5	27	11 ± 1.8		27	29 ± 2.32	
Prothrombin time			**0.046***			**0.041***
<15 sec	26	25 ± 1.7		28	27 ± 2.32	
>15 sec	4	13 ± 1.9		2	11 ± 0.51	
Albumin (g/dl)			0.061			0.241
<3	5	16 ± 4.9		3	12 ± 0.82	
>3	25	46 ± 2.7		27	29 ± 2.31	
Size (cm)			0.576			0.061
<6	11	17 ± 2.8		14	18 ± 7.51	
>6	19	26 ± 1.7		16	31 ± 1.92	
Number			0.061			0.180
Solitary	26	15 ± 6.5		25	18 ± 6.6	
Multiple	4	21 ± 2.4		5	29 ± 2.33	
Capsule			0.106			0.210
Present	11	25 ± 1.7		14	23 ± 6.1	
Absent	19	33 ± 1.9		16	27 ± 3.21	
Grade			**0.007***			**0.001***
High	21	32 ± 1.8		21	30 ± 1.99	
Low	9	25 ± 4.4		9	12 ± 0.71	
Vascular invasion			0.07			**0.0001***
Present	12	13 ± 1.7		15	20 ± 5.45	
Absent	18	21 ± 6.4		15	32 ± 1.79	
Capsular invasion			0.07			0.266
Present	12	13 ± 1.7		3	11 ± 0.61	
Absent	18	21 ± 6.4		27	30 ± 7.1	
Steatosis			0.576			0.082
Present	4	15 ± 1.9		3	20 ± 2.19	
Absent	26	18 ± 2.6		27	29 ± 2.2	
Major resection			0.069			0.351
Yes	17	29 ± 1.92		20	31 ± 6.7	
No	13	21 ± 0.60		10	22 ± 7.1	
Blood transfusion			0.199			**0.012*`**
Yes	2	18 ± 0.09		2	11 ± 0.50	
No	28	31 ± 2.4		28	27 ± 2.31	
Post-op stay			0.659			**0.010***
(days)	19	36 ± 3.1		17	28 ± 1.71	
<15	11	23 ± 2.2		13	11 ± 0.07	
>15						

Wound infection			0.346			**0.021***
Present	6	11 ± 0.50		8	18 ± 2.90	
Absent	24	31 ± 1.91		22	28 ± 2.21	
Sepsis			0.062			**0.001***
Present	6	19 ± 2.96		5	12 ± 2.19	
Absent	24	33 ± 1.71		25	29 ± 2.33	
Post-op liver failure			0.792			**0.023***
Present	3	15 ± 4.6		4	12 ± 0.43	
Absent	27	23 ± 0.79		26	29 ± 2.08	

*p value <0.05 = statistically significant

Table 12: Significant prognostic factors for overall survival by multivariate analysis in 30 patients with non-cirrhotic HCC

Variables	Hazard ratio	95% CI	p-value	Model prediction
High grade tumors	**0.820**	**(0.694-0.698)**	**0.019***	
Bilirubin	1.846	(0.893-3.816)	0.098	
Protrombin time	0 .488	(0.117-2.044)	0.327	46.27

95% CI: 95% confidence interval, *p <0.05 = statistically significant

DISEASE FREE SURVIVAL:

Excluding the post-operative death within 30 days, the overall 1-, 2-, 3- year disease-free survival rates after curative liver resection for HCC in non-cirrhotic patients were 66.6%, 53.3% and 50% respectively.

PROGNOSTIC FACTORS FOR DISEASE-FREE SURVIVAL:

Post-operative deaths within 90-days were excluded from the analysis of prognostic factors for disease-free survival after liver resection for HCC in non-cirrhotic patients. In the univariate analysis, need for blood transfusion (p = 0.012), post-operative liver failure

(p = 0.023), wound infection (p = 0.021), sepsis (p = 0.001), high grade tumor(p = 0.001), vascular invasion (0.0001), prothrombin time (p = 0.041), serum bilirubin (p = 0.012), post-operative length of stay (p = 0.010) significantly affected the disease-free survival (Table-11). The multivariate analysis identified high grade tumors (p = 0.039), vascular invasion (p = 0.002), and sepsis (p = 0.011) as independent prognostic factors for disease free survival (Figure: 7-9) after liver resection for non-cirrhotic HCC patients (Table-13).

Table13: Significant prognostic factors for disease-free survival by multivariate analysis in 30 patients with non-cirrhotic HCC

Variables	Hazard ratio	95% CI	p-value	Model prediction
High grade tumors	**0.092**	**(0.015-0.590)**	**0.039***	
Sepsis	**0.091**	**(0.015-0.574)**	**0.011 ***	
Vascular invasion	**0.073**	**(0.014-0.389)**	**0.002 ***	
Bilirubin	2.289	(0.129-40.550)	0.572	
Prothrombin time	0 253	(0.033-1.935)	0.185	
Blood transfusion	0.134	(0.006-2.774)	0.194	
Hospital stay	0.981	(0.818-1.176)	0.883	
Wound infection	0.283	(0.016-5.136)	0.393	55.70
Post-op liver failure	0.498	(0.671-2.116)	0.469	

95% CI: 95% confidence interval, *p <0.05 = statistically significant

CHARTS

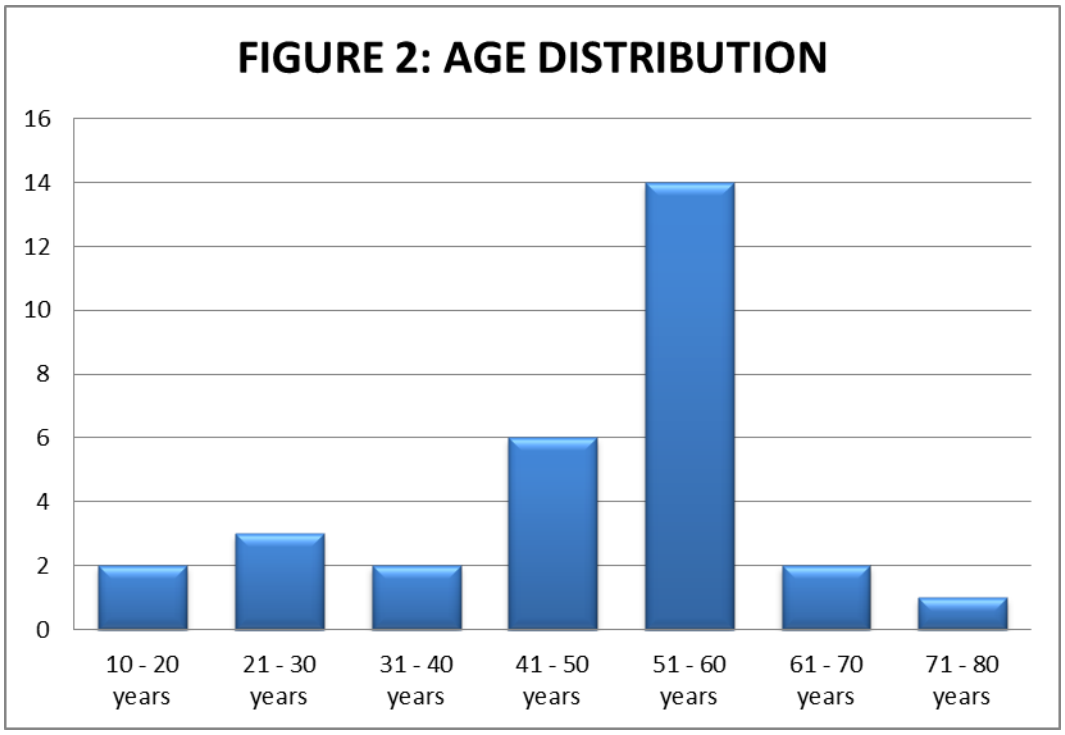


FIGURE 2: AGE DISTRIBUTION
16
14
12
10
8
6
4
2
0
10 - 20 years
21 - 30 years
31 - 40 years
41 - 50 years
51 - 60 years
61 - 70 years
71 - 80 years

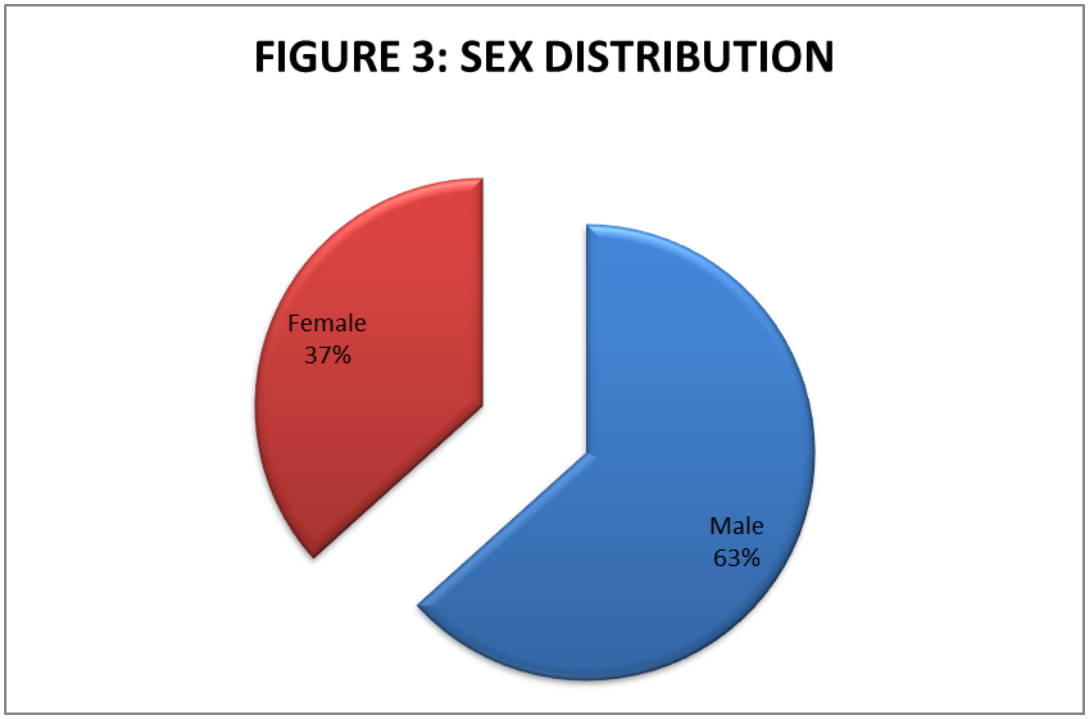


FIGURE 3: SEX DISTRIBUTION
Female 37%
Male 63%

FIGURE 4: OPERATIVE PROCEDURES

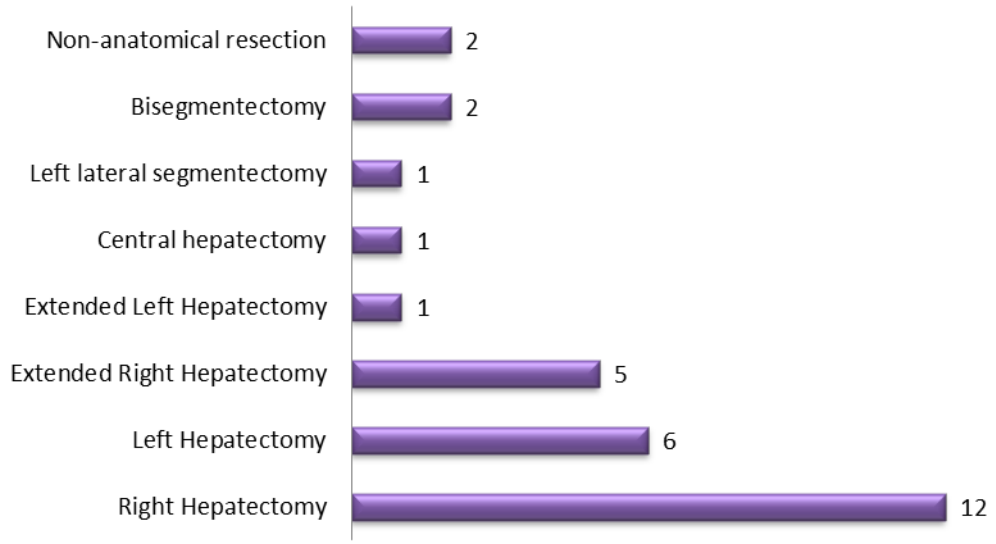


FIGURE 5: POST-OPERATIVE COMPLICATIONS

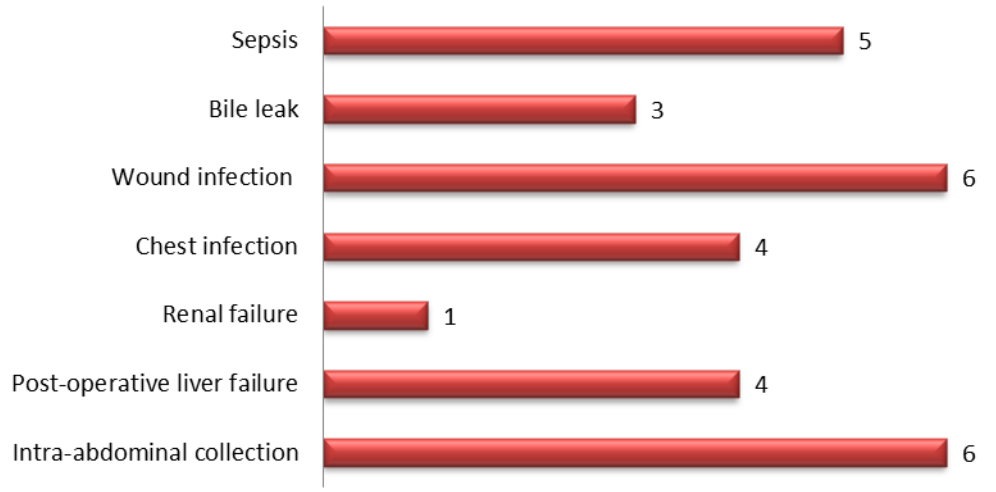


FIGURE 6: Kaplan-Meier curve showing Overall survival of non-cirrhotic patients treated for HCC according to tumor differentiation

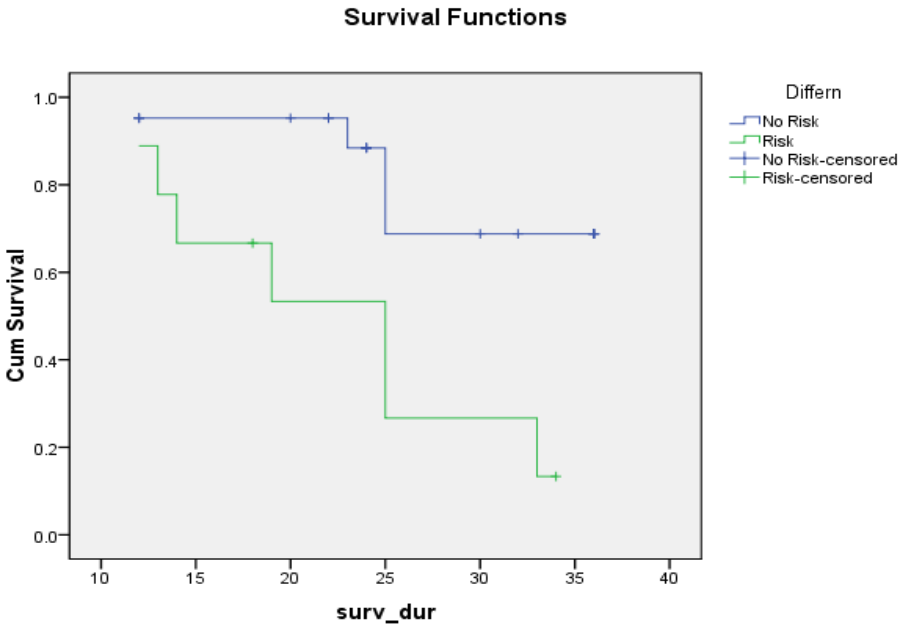


FIGURE 7: Kaplan-Meier curve showing Disease-free survival of non-cirrhotic patients treated for HCC according to tumor differentiation

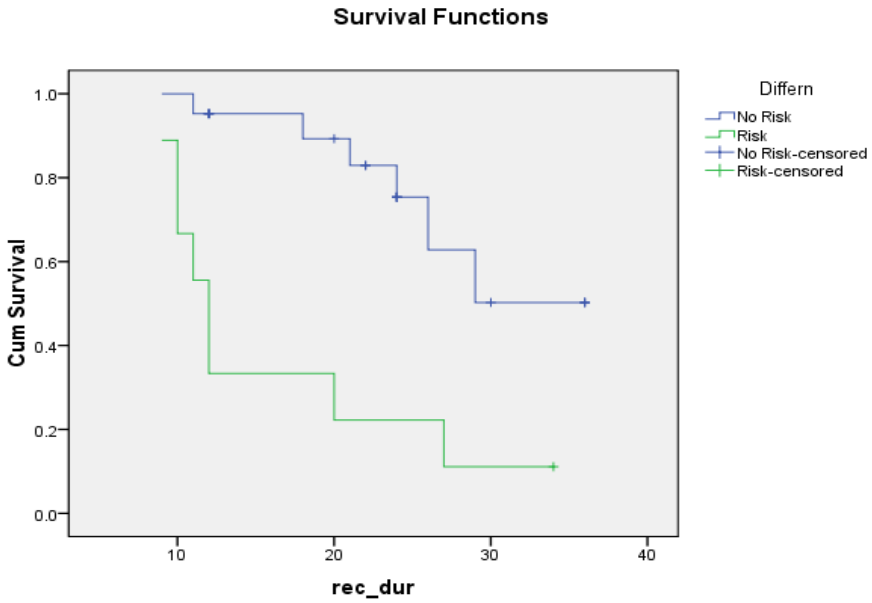


FIGURE 8: Kaplan-Meier curve showing Disease-free survival of non-cirrhotic patients treated for HCC according to sepsis

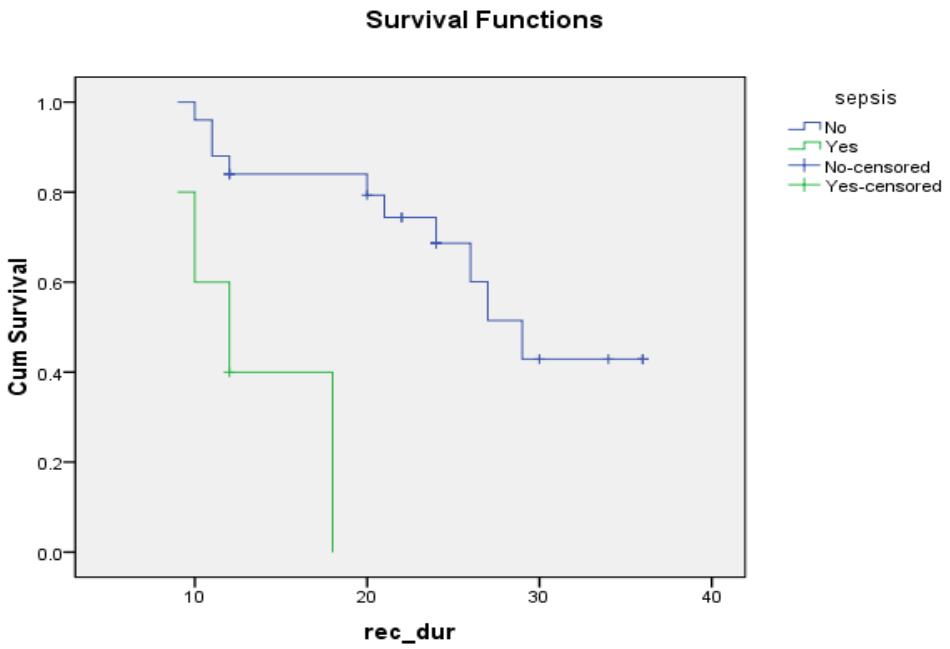


FIGURE 9: Kaplan-Meier curve showing Disease-free survival of non-cirrhotic patients treated for HCC according to Microvascular invasion

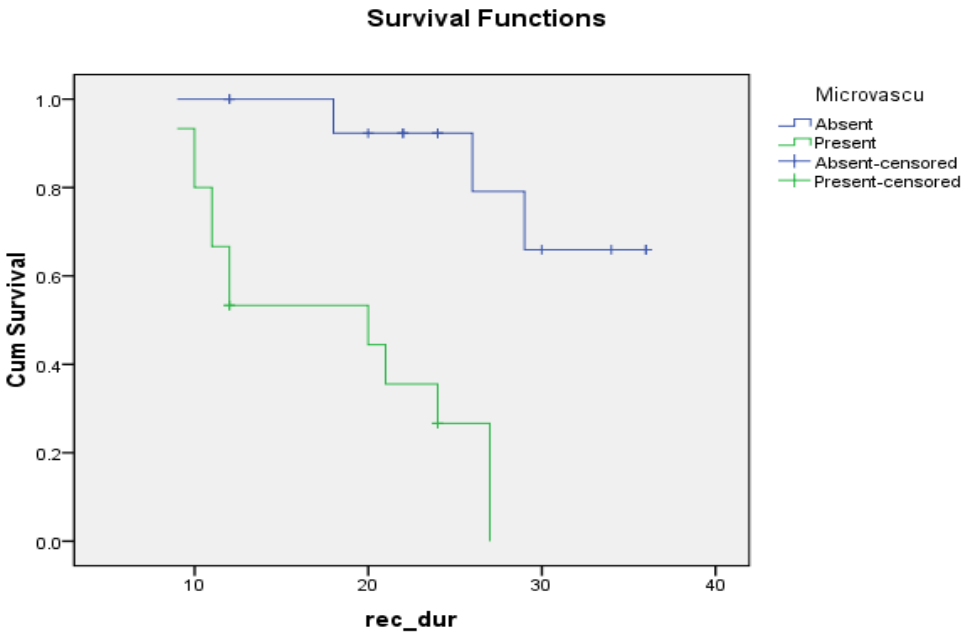


FIGURE 10: Computerized tomography (CT) scan showing HCC in right lobe of non-cirrhotic liver.

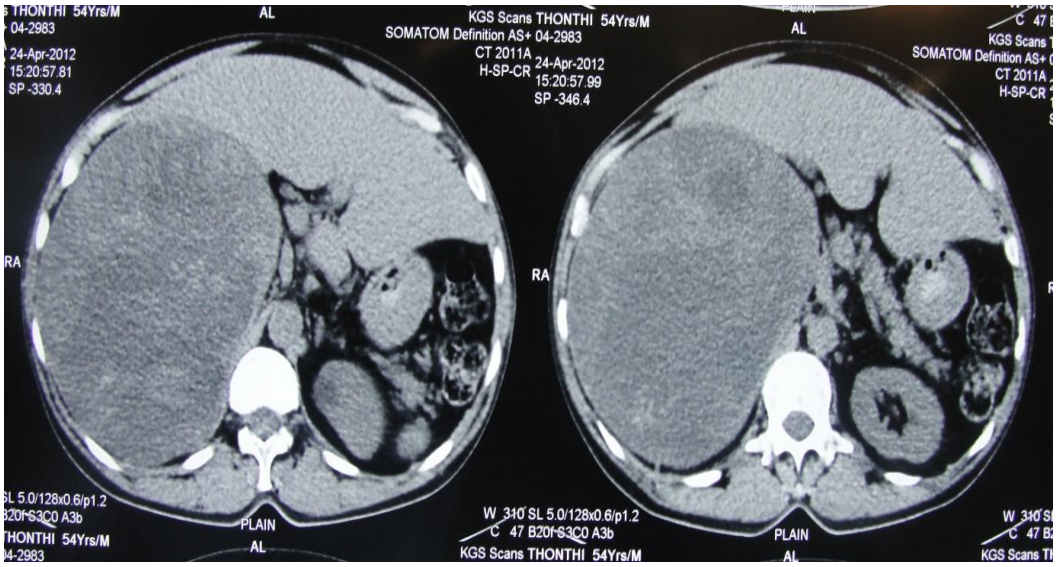
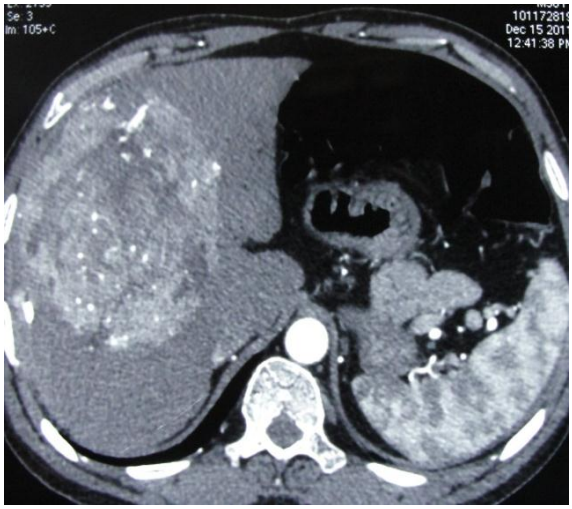


FIGURE 11: CECT showing arterial enhancement in HCC.

FIGURE 12: CECT showing early venous washout in HCC.



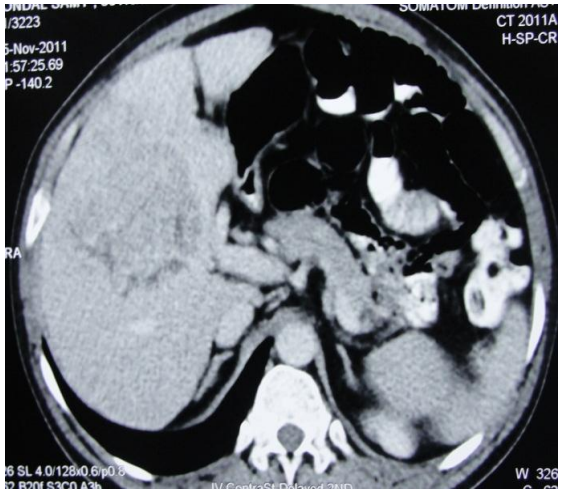


FIGURE 13: Intra-operative photograph showing 20 x 15 cm HCC in right lobe of non-cirrhotic liver

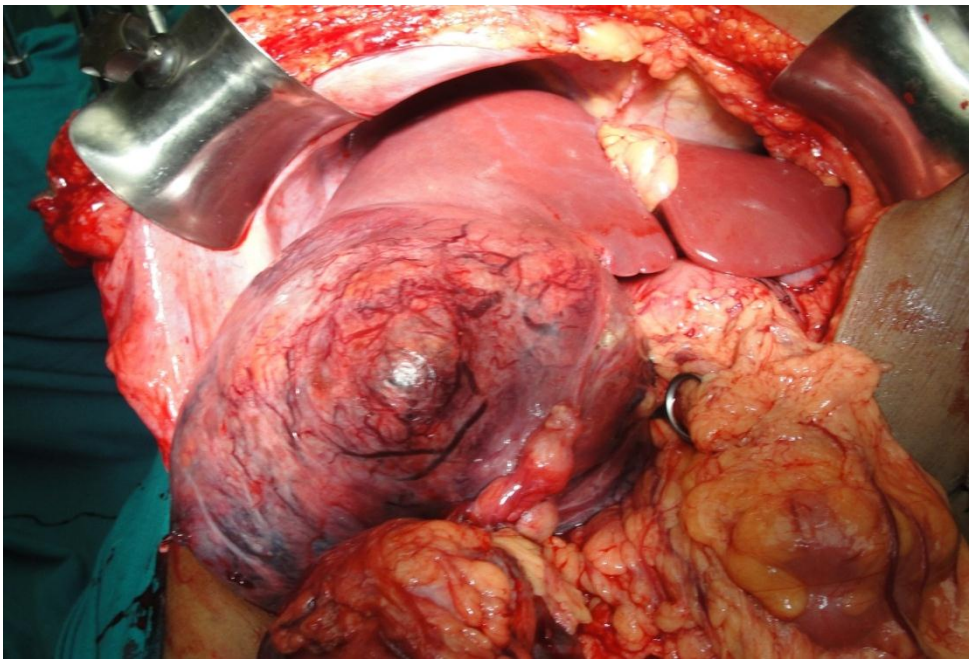


FIGURE 14: Intra-operative photograph showing dissection of right lobe with tumor from inferior vena-cava.

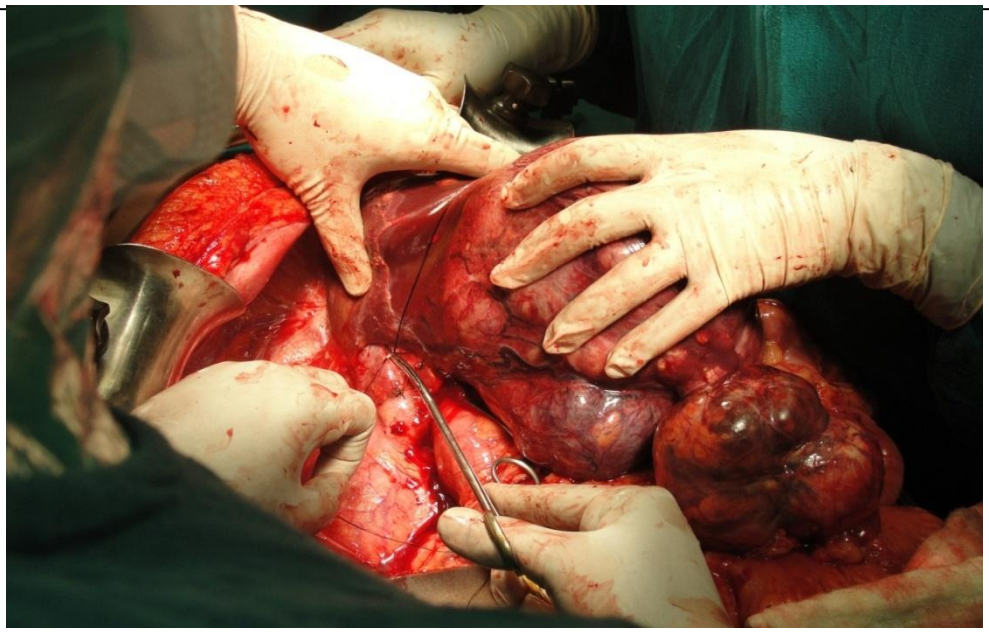


FIGURE 15: Intra-operative photograph showing line of parenchymal transection during right hepatectomy

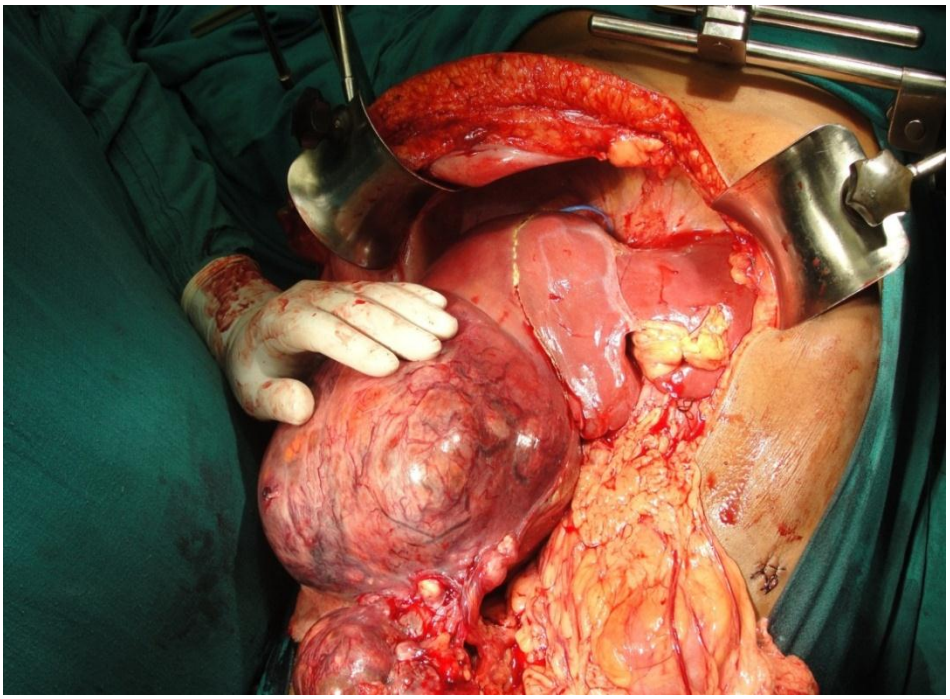


FIGURE 16: The resected specimen after right hepatectomy

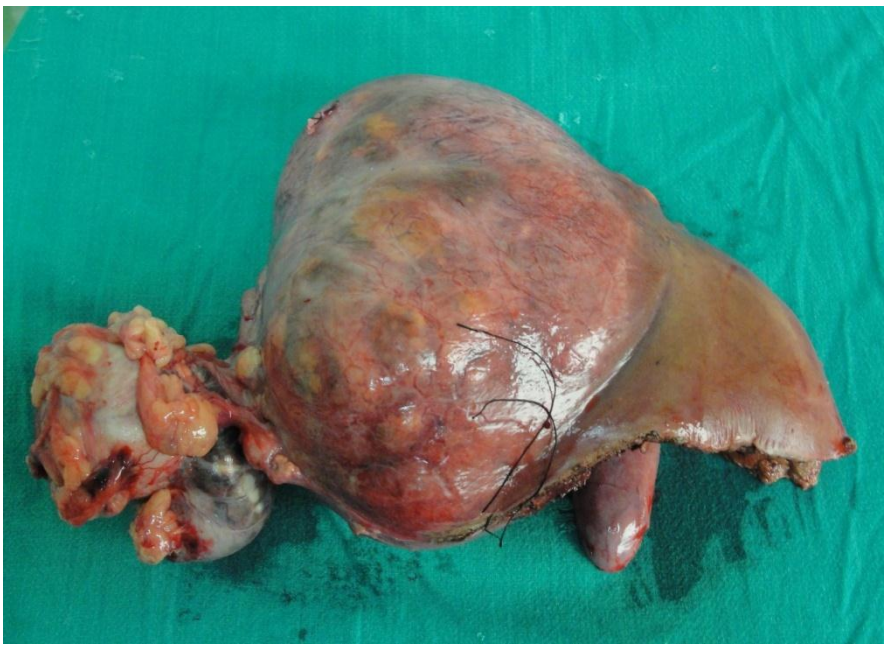


FIGURE 17: Intra-operative photograph showing 8x6cm HCC in left lateral segment of non-cirrhotic liver.

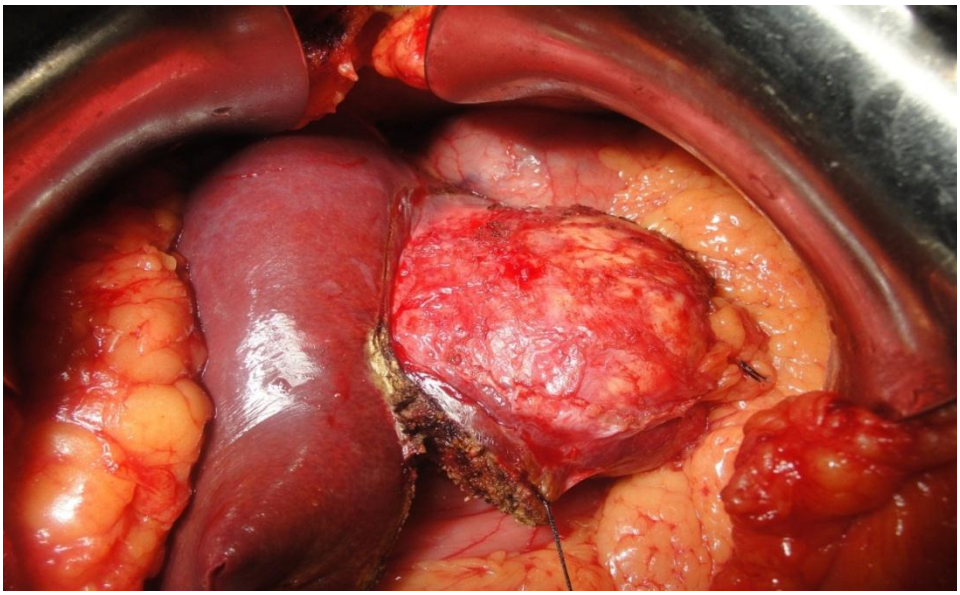


FIGURE 18: The resected specimen after left lateral segmentectomy

DISCUSSION

DISCUSSION

Although most HCC arise in the cirrhotic liver, approximately 10-40% of cases develop in non-cirrhotic, non-fibrotic liver.[104] In our study, we found that HCC in non-cirrhotic liver represented nearly 39% of our resections performed for HCC, thus making it an important clinical entity. Many studies have analyzed the outcomes after liver resection for HCC, however only few studies have focused solely on outcomes after liver resection for HCC in non-cirrhotic, non-fibrotic liver. This study analyze a cohort of 30 non-cirrhotic patients who underwent liver resection for HCC at Institute of surgical gastroenterology and liver transplantation during the period between August 2010 and December 2012 with attention paid to clinico-pathological data and predictors of survival and recurrence.

DEMOGRAPHIC CHARACTERISTICS:

The mean age of HCC in non-cirrhotic patients in our study was 48.3 years, similar to that reported by Bismuth et al and Chang et al, which is about 10 years younger than in cirrhotic patients with HCC. As in previous other reports,[26,27,65] there was a lower male preponderance in our study with male: female ratio of 1.7: 1, compared to 4- 8:1 in cirrhotic patients.

The etiological factors for the development of HCC in non-cirrhotic HCC are not well documented.[105] The well-known fact that HBV infection has direct carcinogenic potential was supported by a small proportion (13%) of patients with HBV infection in our study. Although there are few reports[11,26,29,49] of HCV infection in non-cirrhotic HCC, there were no such patients in our study. Only 30% of our patients are associated alcohol intake, which is concordant with the hypothesis that carcinogenic potential of alcohol is almost entirely due to development of cirrhosis. In accordance with previous studies (Table 1-3), the prevalence of three main risk factors for HCC (HBV, HCV and alcohol) are low in our study, when compared to cirrhotic patients with HCC. There were significant proportion of patients with diabetes mellitus (27%) and obesity (10%) in the present study. This finding appears to be relevant because many recent reports suggest that diabetes and obesity are major risk factors for HCC in non-cirrhotic liver. However, in 40% of patients, the etiology was unknown. Such a high proportion of non-cirrhotic HCC patients without any identifiable etiological factor suggest the possibility of another hitherto unknown factor or pathogenic pathway for non-cirrhotic HCC in Indian patients, which requires further study.

CLINICAL PRESENTATION:

Due to the absence of underlying liver disease in non-cirrhotic patients, HCC is often diagnosed when it has reached a size that produces symptoms.[24] The mean tumor size in our study was 13.2 years, which is more than most reported series (<10 cm) (Table-15). This may possibly due to delay in diagnosis, referral bias or tolerance and neglect of non-specific symptoms by our patients. All the patients in our study presented with pain support the view that most of our patients seek attention only when tumor has grown sufficient size to produce mass-related symptoms.

It is not surprising to note that the laboratory marker of liver function and portal hypertension associated with outcome in cirrhotic patients with HCC did not have any significant influence in non-cirrhotic patients with HCC. This may be partly explained by the poor liver function in cirrhotic patients which precludes safe resection. Several studies[106] have proposed that AFP production depends on the tumor size or differentiation. In contrast, the AFP level was normal in 67% of our patients despite the mean tumor size of 13.2cm and 30% of patients with poorly differentiated tumors. Moreover, an Indian study by Madangopalanet al[107] has shown the prevalence of AFP in HCC was about 51%.

PERI-OPERATIVE OUTCOME:

The site of tumor location, extent of resection was almost similar to previous studies, as summarized in table-14. However the operative time, blood loss and transfusion requirements were low when compared to the older studies. This might be explained by the availability of modern technology (Harmonic scalpel, CUSA, waterjet), improved surgical skills, advanced anaesthesia and operations performed in highly specialized center. Like most other studies (Table-14), none of the peri-operative parameters were found to be significantly associated with outcome after liver resection of non-cirrhotic HCC in the present study.

Table 14: Comparison ofperi-operative results with previous other studies.

Authors	**n**	**Right lobe tumors (%)**	**Major liver resection**	**Operative time (mins)**	**Mean Blood loss (ml)**	**Blood transfusion(%)**	**Mean Post-operative stay**	**Post-operative complication rate (%)**	**Operative mortality (%)**
Bimuth et al[7]	68	61	82	NR	NR	NR	NR	19	2.9
Shimada et al[29]	65	NR	57	315	1396	NR	30	24.6	0
Poon et al[12]	155	NR	80	NR	2200	55	NR	39	4.5
Nagasue et al[10]	100	38	58	148	913	NR	30	22	3
Grazi et al[11]	135	NR	87	NR	NR	25	10	26	3
Chang et al[9]	223	39	47	NR	NR	18	13	31	1.3

Laurent et al[105]	108	NR	61	NR	750	32	14	23	6.5
Dupont-Bierre et al[4]	84	54	85	NR	NR	NR	NR	26.2	3.6
Taura et al[85]	127	NR	38	293	830	38	NR	32	2
Lang et al[17]	80	42	69	NR	NR	0	NR	NR	6
Rayya et al[113]	55	54	74	NR	NR	NR	18	34	6
Shrager et al[108]	206	50	72	NR	NR	32	NR	NR	2.9
Thelen et al[110]	110	45	61	NR	NR	NR	15	NR	NR
Our study	30	63	83	165	220	6.7	16	50	3.4

NR: Not Reported

POST-OPERATIVE COMPLICATIONS:

In the present study, one patient (3.4%) died in the post-operative period due to post-hepatectomy liver failure following extended right hepatectomy. The post-operative morbidity rate in our study (50%) was higher than most reported series (19%-39%). The high post-operative morbidity in the present study possibly suggests the inevitable consequence of the major resections (83%) performed for large tumors (mean size: 13.2cm) in non-cirrhotic patients.

The most common complication in our study was intra-abdominal collection and wound infection followed by sepsis and post-operative liver failure. Sepsis was found to be an independent prognostic factor for disease-free survival in our study. The reason behind this finding is not clear. However, what is clear is that improved survival does not stem from the differences in recurrence.

HISTOPATHOLOGICAL CHRACTERISTICS:

The mean tumor size in our study (13.2 cm) was higher than the other studies in literature (table-15). Similar to Poon et al[12] and Shrager et al[108], the positive surgical margin in our study was less (26.7%) in comparison with previous studies. However, the multi-nodularity, tumor capsule formation, tumor differentiation and vascular invasion were similar to most other reported series(table-15).

Table 15: Comparison of histo-pathological characteristics with previous other studies

Authors	n	Mean tumor size (cm)	Multiple tumors (%)	Capsule present (%)	High grade tumor (%)	Margin positivity (%)	Microvascular invasion (%)
Bimuth et al[7]	68	8.8	12	76	82	NR	46
Shimada et al[29]	65	5.4	NR	86	63	33.8	50.7
Poon et al[12]	155	NR	25	45	66	9	45
Nagasue et al[10]	100	NR	19	71	82	32	38
Grazi et al[11]	135	7.9	12.6	31.1	39	NR	53.3
Chang et al[9]	223	7.1	NR	46.2	82.1	47	62
Laurent et al[105]	108	9.3	20.3	64	49	52	24
Dupont-Bierre et al[4]	84	8.5	21.4	57	69.6	37.7	39.1
Taura et al[85]	127	NR	16	NR	63	NR	24
Lang et al[17]	80	8	21.2	NR	75.7	NR	48.4
Rayya et al[113]	55	8.2	29	NR	86	NR	NR
Shrager et al[108]	206	8.2	15.5	NR	79.5	9	70
Thelen et al[110]	110	7.8	30.9	NR	89	NR	39
Our study	30	13.2	23	63.3	69.7	26.7	50

NR: Not Reported

The important negative prognostic factors predicting survival in the literature are large tumor size, vascular invasion, positive surgical margin, multi-nodularity, tumor differentiation (table-16). In the present study, tumor differentiation was found to be independent predictor for both poor survival and earlier recurrence whereas vascular invasion was significant negative prognostic factor for early recurrence.

OUTCOMES AND PREDICTIVE FACTORS FOR SURVIVAL AND RECURRENCE:

Surgical therapy, either liver resection or transplantation, remains the gold standard in the curative treatment of HCC. Numerous studies have shown that liver resection is the treatment of choice for patients with non-cirrhotic HCC. In our study, the overall survival rate of non-cirrhotic HCC was 86.7%, 66.7% and 63.3% at 1-, 2- and 3-years after curative resection respectively, comparable with the results of other studies (table-16). It is important to note that such high survival rate and cure are achieved only rarely with non-surgical treatment for non-cirrhotic HCC and even with newer innovative approaches such as SIRT (Selective internal radiation therapy), long-term survival is observed only exceptionally.[109] This highlights the pivotal role of liver resection in non-cirrhotic patients with HCC and should be aimed for in all resectable tumors.

The disease-free survival after liver resection for non-cirrhotic HCC ranges between 31-56% and 24-61% at 3- and 5-year respectively in the literature (table-16).

Table 16: Comparison of survival and recurrence with other studies.

Authors	n	Recurrence rate (%)	Overall survival (%)			Disease-free survival (%)			Independent predictive factor for poor survival and early recurrence
			1y	3y	5y	1y	3y	5y	
Bimuth et al[7]	68	59	74	52	40	70	43	33	Size>9cm, vascular invasion
Shimada et al[29]	65	NR	NR	75	65	NR	56	38	NR
Poon et al[12]	155	51	80	59	46	57	42	35	NR
Nagasue et al[10]	100	51	97	76	50	79	38	31	Vascular invasion, HCV positivity, positive surgical margin, satellitosis, major resection
Grazi et al[11]	135	30	84	68	51	78	58	46	Blood transfusion, age>60 years
Chang et al[9]	223	59	NR	NR	53	NR	NR	37	TNM stage
Laurent et al[105]	108	52	NR	43	29	NR	55	43	Satellitosis, absent capsule, Blood transfusion, positive surgical margin
Dupont-Bierre et al[4]	84	39	78	55	44	73	49	49	Multiple tumors, vascular invasion, non-use ofadjuvant iodine-131 oil

Taura et al[85]	127	54	NR	NR	81	NR	NR	NR	No independent predictors
Lang et al[17]	80	63	77	38	NR	NR	NR	NR	Vascular invasion, grade, positive surgical margin
Rayya et al[113]	55	73	69	48	48	NR	NR	NR	NR
Shrager et al[108]	206	52	60	46	NR	NR	61	NR	Large size, satellitosis, vascular invasion, raised AFP
Thelen et al[110]	110	NR	84	66	50	69	53	42	R1/2 resection, growth pattern, large & multiple tumor
Our study	30	46.6	86.6	63.3	-	66.6	50	-	High grade tumors, vascular invasion, sepsis

NR: Not Reported, HCV: Hepatitis C virus, TNM: tumor-node-metastasis stage, AFP: Alpha-fetoprotein.

In a recent study by Thelenet al[110] (2013), the disease-free survival at 3-year and 5-year was 53% and 42%. Similarly, in the present study, the 3-year disease-free survival was 50%.

Bismuth et al[7] has shown a recurrence rate of 59% in non-cirrhotic patients with HCC during follow-up. Intrahepatic, extra-hepatic and both intra & extra-hepatic recurrences were 44%, 15%, 8% respectively. Similarly, Dupont-Bierreet al[4] has found a recurrence rate of 41% recurrence after liver resection for non-cirrhotic HCC. The intrahepatic, extra-hepatic and both intra & extra-hepatic recurrences were 52%, 11%, 37% respectively. The recurrence rate in our study was 50% and the intrahepatic, extra-hepatic and both intra & extra-hepatic

recurrences were 38%, 21%, 43% respectively, which is in accordance with previous studies. The hypothesis that most early recurrences result from metastatic spread rather than de novo origin[111] was supported by the finding that more than 85% recurrences were detected within first year. This data highlights the necessity of strict surveillance in the first 2 years to identify early recurrence after liver resection in non-cirrhotic HCC and thereby perform potentially benefitting surgical re-resection.

Several prognostic factors that may affect the outcome after liver resection for non-cirrhotic HCC were summarized in table-16. Among the different predictive factors in different studies, the most constant independent predictor for poor survival and early recurrence are large tumor size, vascular invasion, positive surgical margin, multi-nodularity, tumor differentiation.

In the present study, the only independent predictive factor for poor survival after liver resection non-cirrhotic HCC in both univariate and multivariate analysis was high tumor grade. Similarly, the independent predictive factors for early recurrence in both univariate and multivariate analysis were high tumor grade, vascular invasion, and sepsis. Since vascular infiltration was associated with large tumor size, high grade and multifocality in this study, a combination of tumor size, grade and number of tumor may be regarded as surrogate marker of vascular infiltration.

To conclude, we noticed a lower male preponderance and lower prevalence of main risk factors (HBV, HCV, Alcohol) in patients with non-cirrhotic HCC. In spite of delayed presentation and large tumor size, major resection can be performed safely in non-cirrhotic HCC patients. Vascular invasion, tumor differentiation and sepsis are identified as poor prognostic factors after liver resection in patients with non-cirrhotic HCC. However, a larger study may be required to confirm this hypothesis.

LIMITATIONS OF THE STUDY:

1. Small study population
2. Short period of the study

In the small cohort of 30 patients with non-cirrhotic HCC, we could identify clinic-pathological differences between cirrhotic and non-cirrhotic patients with HCC as well as assess outcome and prognostic factors for survival and recurrence. Moreover, inspite of above limitation, the present study lays foundation for future long-term and large prospective study.

CONCLUSION

CONCLUSION

The present study confirms that HCC can occur in the absence of cirrhosis (40%) and without known risk factors (40%). In this setting, HCC is more likely to present as large symptomatic mass in a middle-aged person with lower male preponderance and low prevalence of three major risk factors (HBV, HCV and alcohol), when compared to HCC in cirrhotic patients.

Inspite of large tumor size at presentation, liver resection can be performed safely in non-cirrhotic patients with HCC with acceptable morbidity and mortality and resection should be attempted whenever feasible.

This study demonstrated that tumor differentiation (high grade tumor) is the only predictor of overall survival in non-cirrhotic patients with HCC. Vascular invasion, high grade tumor and sepsis are independent predictors of early recurrence in non-cirrhotic HCC patients. The presence of these poor prognostic factors in non-cirrhotic HCC patients necessitates a stringent follow-up to detect and treat recurrence.

However, a large sample size and follow-up of this subset of patients for 10 or more years could help to confirm the role of vascular invasion, tumor differentiation and sepsis as poor prognostic factors and identify other factors as long-term prognostic indicators in patients with non-cirrhotic HCC.

BIBLIOGRAPHY

BIBLIOGRAPHY

1. Sherman M. Epidemiology of hepatocellular carcinoma. Oncology. 2010;78:7–10.

2. Parkin DM, Bray F, Ferlay J. Global cancer statistics 2002 CA Cancer J Clin 2005;55:7: 4-108

3. Trinchet JC, Beaugrand M, Augmentation de l'incidence du carcinoma hepato-cellulairedans les pays occidentaux. GastroenterolClinBiol 1999;23:1286-1288.

4. Dupont-Bierre E, Compagnon P, Raoul J, Fayet G, Laarte-Thirourd A Boudjema K. Resection of hepatocellular carcinoma in Noncirrhotic liver: Analysis of risk factors for survival. J Am CollSurg 2005;201:663-670.

5. Bruix J, Sherman M, Llovet JM. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the study of the liver. J Hepatol 2001;35:421-430.

6. Houben KW, McCall JL. Liver transplantation for hepatocellular carcinoma in patients without underlying liver disease: asystematic review. Liver TransplSurg 1999;5:91-95.

7. Bismuth H, Chiche L, Castaing D. Surgical treatment of hepatocellular caicinoma in noncirrhotic liver: experience with liver resections. World J Surg 1995;19:35-41

8. Thelen A, Benckert C, Tautenhahn HM, Hau HM, Bartels M, Linnemann et al. Liver resection for hepatocellular carcinoma in patients without cirrhosis. British journal of surgery 2013;100:130-137.

9. Chang CH, Chau GY, Lui WY, Tsay SH, King KL, Wu CW. Long term results of hepatic resection for hepatocellular carcinoma originating from the non-cirrhotic liver. Arch Surg 2004;139:320-325.

10. Nagasue N, Ono T, Yamanoi A, Kohno H, El-Assal ON, Taniura H, Uchida M. Prognostic factors and survival after hepatic resection for hepatocellular carcinoma without cirrhosis. British journal of surgery 2001;88:515-522.

11. Grazi GL, Cescon M, Ravaioli, Ercolani G, Gardini A, Del Gaudio M, Vetrone G, Cavallari A. Liver resection for hepatocellular carcinoma in cirrhotics and non-cirrhotics. Evaluation of clinicopathological features and comparison of risk factors for long-term survival and tumor recurrence in a single centre. Aliment PharmacolTher 2003;17:119-129.

12. Poon RT, Fan ST, Ng IO, et al. Different risk factors and prognosis for early and late intrahepatic recurrence after resection of hepatocellular carcinoma. Cancer 2000;89:500–507.

13. Poon RT, Fan ST, Lo CM, et al. Improving survival results after resection of hepatocellular carcinoma: a prospective study of 377 patients over 10 years. Ann Surg 2001;234:63–70.

14. Ikai I, Arii S, KojiroM, et al. Reevaluation of prognostic factor for survival after liver resection in patients with hepatocellular carcinoma in a Japanese nationwide survey. Cancer 2004;101: 796–802.

15. Belghiti J, Regimbeau JM, Durand F, et al. Resection of hepatocellular carcinoma: A European experience on 328 cases. Hepatogastroenterology 2002;49:41–46.

16. Regimbeau JM, Abdalla EK, Vauthey JN, et al. Risk factors for early death due to recurrence after liver resection for hepatocellular carcinoma: results of a multicenter study. J SurgOncol 2004;85:36–41.

17. Lang H, Sotiropoulos GC, Domland M, Fruhauf NR, Paul A, Husing J, Malago M and Broelsch CE. Liver resection for hepatocellular carcinoma in non cirrhotic liver without underlying viral hepatitis. British Journal of surgery 2005;92:198-202.

18. Bruix J, Sala M, Llovet JM. Hepatocellar carcinoma. In: Blumgart LH, editor. Surgery of the liver, Biliary tract, and Pancreas, 4th ed. Philadelphia: Saunders Elsevier; 2007. p. 1152-58.

19. Bruix J, Sherman M, Liovet JM, Beaugrand M, Lencioni R, Burrough AK et al. EASL Panel of experts on HCC. EASL-EORTC clinical practice guidelines: Management of hepatocellular carcinoma. J Hepatol 2012;56:908-43.

20. Bosch FX. Global epidemiology of hepatocellular carcinoma. In: Okuda K, Tabor E, eds. Liver Cancer. New York, Churchill Livingstone, 1997:13–27.

21. Kumar R, Sraswat MK, Sharma BC, Sakuja P, Sarin SK. Characteristics of hepatocellular carcinoma in India: a retrospective analysis of 191 cases. Q J Med 2008;101:479-485.

22. Annual Report 1987. National Cancer Registry Programme.New Delhi, Indian Council of Medical Research, 1990.

23. Annual Report 1987. National Cancer Registry Programme. New Delhi, Indian Council of Medical Research, 1990.

24. Trevisani F, Frigerio M, Santi V, Grignashi A, Bernadi M. Hepatocellular carcinoma in non-cirrhotic liver: A reappraisal. Digestive and liver disease 2010;42:341-47.

25. Okuda K, Nakashima T, Kojiro M, et al. Hepatocellular carcinoma without cirrhosis in Japanese patients. Gastroenterology 1989;97:140–6.

26. Trevisani F, D'Intino PE, Caraceni P, et al. Etiologic factors and clinical presentation of hepatocellular carcinoma. Differences between cirrhotic and noncirrhotic Italian patients. Cancer 1995;75:2220–32.

27. Nzeako UC, Goodman ZD, Ishak KG. Hepatocellular carcinoma in cirrhotic and noncirrhotic livers. A clinico-histopathologic study of 804 North American patients. Am J ClinPathol 1996;105:65–75.

28. National Coordination Group of Pathology of Liver Cancer. Relationship between hepatocellular carcinoma, liver cirrhosis, and hepatitis B: a pathological study. Natl Med J China 1982;62:257–61.

29. Shimada M, Rikimaru T, Sugimachi K, et al. The importance of hepatic resection for hepatocellular carcinoma originating from nonfibrotic liver. J Am CollSurg 2000;191:531–7.

30. Farazi PA, DePinho RA. Hepatocellular carcinoma pathogenesis: from genes to environment. Nat Rev Cancer 2006;6:674–87.

31. Liu CJ, Chen BF, Chen PJ, et al. Role of hepatitis B virus precore/core promoter mutations and serum viral load on noncirrhotic hepatocellular carcinoma: a case–control study. J Infect Dis 2006;194:594–9.

32. Yuen MF, Tanaka Y, Shinkai N, et al. Risk for hepatocellular carcinoma with respect to hepatitis B virus genotype B/C, specific mutations of enhancer II/core promoter/precore regions and HBV DNA levels. Gut 2008;57:98–102.

33. Guo X, Jin Y, Qian G, et al. Sequential accumulation of the mutations in core promoter of hepatitis B virus is associated with the development of hepatocellular carcinoma in Qidong, China. J Hepatol 2008;49:718–25.

34. Yoshida H, Shiratori Y, Moriyama M, et al. Interferon therapy reduces the risk for hepatocellular carcinoma: national surveillance program of cirrhotic and noncirrhotic patients with chronic hepatitis C in Japan. IHIT Study Group.Inhibition of Hepatocarcinogenesis by Interferon Therapy. Ann Intern Med1999;131:174–81.

35. Bruix J, Sherman M. Management of hepatocellular carcinoma. Hepatology 2005;42:1208–36.

36. Ray RB, Meyer K, Ray R. Hepatitis C virus core protein promotes immortalization of primary human hepatocytes. Virology 2000;271:197–204.

37. Sakamuro D, Furukawa T, Takegami T. Hepatitis C virus nonstructural protein NS3 transforms NIH 3T3 cells. J Virol 1995;69:3893–6.

38. El-Refaie A, Savage K, Bhattacharya S, et al. HCV-associated hepatocellular carcinoma without cirrhosis. J Hepatol 1996;24:277–85.

39. Makiyama A, Itoh Y, Kasahara A, et al. Characteristic of patients with chronic hepatitis C who develop hepatocellular carcinoma after a sustained response to interferon therapy. Cancer 2004;101:1616–22.

40. Ikeda M, Fujiyama S, Tanaka M, et al. Risk factors for development of hepatocellular carcinoma in patients with chronic hepatitis C after sustained response to interferon. J Gastroenterol 2005;40:148–56.

41. De Mitri MS, Poussin K, Baccarani P, et al. HCV-associated liver cancer without cirrhosis. Lancet 1995;345:413–5.

42. Adami HO, Hsing AW, Mclaughlin JK, et al. Alcoholism and liver cirrhosis in the etiology of primary liver cancer. Int J Cancer 1992;51:898–902.

43. London WT, McGlynn KA. Liver cancer. In: Schottenfeld D, FraumeniJr JF, editors. Cancer epidemiology and prevention. New York: Oxford University Press; 1996. p. 772–93.

44. Reiter E, Zentek J, Razzazi E. Review on sample preparation strategies and methods used for the analysis of aflatoxins in food and feed. MolNutr Food Res 2009;53:508–24.

45. Qian GS, Ross RK, Yu MC, et al. A follow-up study of urinary markers of aflatoxin exposure and liver cancer risk in Shanghai, People's Republic of China.CancerEpidemiol Biomarkers Prev 1994;3:3–10.

46. Ming L, Thorgeirsson SS, Gail MH, et al. Dominant role of hepatitis B virus and cofactor role of aflatoxin in hepatocarcinogenesis in Qidong, China. Hepatology 2002;36:1214–20.

47. Lipshutz GS, Brennan TV, Warren RS. Thorotrast-induced liver neoplasia: a collective review. J Am CollSurg 2002;195:713–8.

48. Turlin B, Juguet F, Moirand R, et al. Increased liver iron stores in patients with hepatocellular carcinoma developed on a noncirrhotic liver. Hepatology 1995;22:446–50.

49. Bralet MP, Régimbeau JM, Pineau P, et al. Hepatocellular carcinoma occurring in nonfibrotic liver: epidemiologic and histopathologic analysis of 80 French cases. Hepatology 2000;32:200–4.

50. Sorrentino P, D'Angelo S, Ferbo U, et al. Liver iron excess in patients with hepatocellular carcinoma developed on non-alcoholic steato-hepatitis. J Hepatol 2009;50:351–7.

51. Rudnick DA, Perlmutter DH. Alpha-1-antitrypsin deficiency: a new paradigm for hepatocellular carcinoma in genetic liver disease. Hepatology 2005;42:514–21.

52. Johnson FL, Feagler JR, Lerner KG, et al. Association of androgenic anabolic steroid therapy with development of hepatocellular carcinoma. Lancet1972;16:1273–6.

53. Farrell GC, Joshua DE, Uren RF, et al. Androgen-induced hepatoma. Lancet 1975;22:430–2.

54. Neuberger J, Forman D, Doll R, et al. Oral contraceptives and hepatocellular carcinoma. Br Med J 1986;292:1355–7.

55. Forman D, Vincent TJ, Doll R. Cancer of the liver and the use of oral contraceptives. Br Med J 1986;292:1357–61.

56. Zucman-Rossi J, Jeannot E, Nhieu JT, et al. Genotype-phenotype correlation in hepatocellular adenoma: new classification and relationship with HCC. Hepatology 2006;43:515–24.

57. Bioulac-Sage P, Rebouissou S, Thomas C, et al. Hepatocellular adenoma subtype classification using molecular markers and immunohistochemistry. Hepatology 2007;46:740–8.

58. Hassan MM, Spitz MR, Thomas MB, et al. The association of family history of liver cancer with hepatocellular carcinoma: a case–control study in the United States. J Hepatol 2009;50: 334–41.

59. Chaubert P, Gayer R, Zimmermann A, et al. Germ-line mutations of the p16 INK4 (MTS1) Gene Occur in a subset of patients with hepatocellular carcinoma. Hepatology 1997;25:1376–81.

60. Tannapfel A, Wittekind C. Genes involved in hepatocellular carcinoma: deregulation in cell cycling and apoptosis. Virchows Arch 2002;440:345–52.

61. Chiappini F, Gross-Goupil M, Saffroy R, et al. Microsatellite instability mutator phenotype in hepatocellular carcinoma in non-alcoholic and non-virally infected normal livers. Carcinogenesis 2004;25:541–7.

62. Togni R, Bagla N, Muiesan P, et al. Microsatellite instability in hepatocellular carcinoma in non-cirrhotic liver in patients older than 60 years. Hepatol Res 2009;39:266–73.

63. Grando-Lemaire V, Guettier C, Chevret S, et al. Hepatocellular carcinoma without cirrhosis in the West: epidemiological factors and histopathology of the non-tumorous liver. Grouped'Etudeet de Traitement du CarcinomeHépatocellulaire. J Hepatol 1999;31:508–13.

64. Stroffolini T, Sagnelli E, Mariano A, et al. Characteristics of hepatocellular carcinoma in Italy. J Hepatol 1998;29:944–52.

65. Smalley SR, Moertel CG, Hilton JF, et al. Hepatoma in the noncirrhotic liver. Cancer 1988;62:1414–24.

66. Capussotti L, Muratore A, Amisano M, et al. Liver resection for large-size hepatocellular carcinomas in 47 non-cirrhotic patients—no mortality and long-term survival. Hepatogastroenterology 2006;53:768–72.

67. Xu L, Huang L, Li BK, et al. Clinicopathologic features and long-term outcomes of Chinese patients with hepatocellular carcinoma in non-cirrhotic liver. Dig Surg 2008;25:376–82.

68. Okamura N, Yoshida M, Shibuya A, et al. Cellular and stromal characteristics in the scirrhous hepatocellular carcinoma: comparison with hepatocellular carcinomas and intrahepatic cholangiocarcinomas. PatholInt 2005;55:724–31.

69. Kassahun WT, Hauss J. Management of combined hepatocellular and cholangiocarcinoma. Int J ClinPract 2008;62:1271–8.

70. Abulkhir A, Limongelli P, Healy AJ. Preoperative portal vein embolization for major liver resection: a meta-analysis. Ann Surg 2008;247:49-57.

71. Wu CC, Ho YZ, Ho WL. Preoperative transcatheter arterial chemoembolization for resectable large hepatocellular carcinoma. Br J Surg 1995;82:122-126.

72. Hanazaki K, Kajikawa S, Shimozawa N, Mihara M, Shimada K, Hiraguri M, Koide N, Adachi W, Amano J. Survival and recurrence after hepatic resection of 386 consecutive patients with hepatocellular carcinoma. J Am CollSurg 2000;191:381-8

73. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A, editors. AJCC Cancer Staging Handbook. 7th ed. New York: Springer; 2010.

74. Llovet JM, Brú C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis 1999;19:329–338.

75. The Cancer of the Liver Italian Program (CLIP) Investigators. A new prognostic system for hepatocellular carcinoma: a retrospective study of 435 patients. Hepatology 1998;28:751–755.

76. Chevret S, Trinchet JC, Mathieu D, Rached AA, Beaugrand M, Chastang C. A new prognostic classification for predicting survival in patients with hepatocellular carcinoma. Grouped'Etudeet de Traitement du CarcinomeHépatocellulaire. J Hepatol 1999;31:133–141.

77. Leung TW, Tang AM, Zee B, Lau WY, Lai PB, Leung KL, et al. Construction of the Chinese University Prognostic Index for hepatocellular carcinoma and comparison with the TNM staging system, the Okuda staging system, and the Cancer of the Liver Italian Program staging system: a study based on 926 patients. Cancer 2002;94:1760–1769.

78. Kitai S, Kudo M, Minami Y, Haji S, Osaki Y, Oka H, et al. Validation of a new prognostic staging system for hepatocellular carcinoma: a comparison of the biomarker-combined Japan Integrated Staging Score, the conventional Japan Integrated Staging Score and the BALAD Score. Oncology 2008;75:S83–S90.

79. Llovet JM, Di Bisceglie AM, Bruix J, Kramer BS, Lencioni R, Zhu AX, et al. Design and endpoints of clinical trials in hepatocellular carcinoma. J Natl Cancer Inst 2008;100:698–711.

80. Makuuchi M, Mori T, Gunven P, et al. Safety of hemihepatic vascular occlusion during resection of the liver. SurgGynecolObstet 1987;164:155–8.

81. Hu RH, Lee PH, Yu SC, et al. Surgical resection for recurrent hepatocellular carcinoma: prognosis and analysis of risk factors. Surgery 1996;120:23–9.

82. Lubrano J, Huet E, Tsilividis B, et al. Long-term outcome of liver resection for hepatocellular carcinoma in noncirrhoticnonfibrotic liver with no viral hepatitis or alcohol abuse. World J Surg 2008;32:104–9.

83. Bège T, Le Treut YP, Hardwigsen J, et al. Prognostic factors after resection for hepatocellular carcinoma in nonfibrotic or moderately fibrotic liver. A 116-case European series. J GastrointestSurg 2007;11:619–25.

84. Sasaki Y, Imaoka S, Masutani S, et al. Influence of coexisting cirrhosis on long-term prognosis after surgery in patients with hepatocellular carcinoma.Surgery 1992;112:515–21.

85. Taura K, Ikai I, Hatano E, et al. Influence of coexisting cirrhosis on outcomes after partial hepatic resection for hepatocellular carcinoma fulfilling the Milan criteria: an analysis of 293 patients. Surgery 2007;142:685–94.

86. Camma et al, 2002. Camma C, et al: Transarterial chemoembolization for unresectable hepatocellular carcinoma:

meta-analysis of randomized controlled trials. *Radiology* 2002; 224:47-54

87. Llovet JM, et al: Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. *Lancet* 2002; 359:1734-1739.

88. Grouped'Etudeet de Traitement du CarcinomeHépatocellulaire, 1995. Grouped'Etude et de Traitement du Carcinome Hépatocellulaire : A comparison of Lipiodol chemoembolization and conservative treatment for unresectable hepatocellular carcinoma. *N Engl J Med* 1995; 332:1256-1261.

89. Pelletier G, et al: A randomized trial of hepatic arterial chemoembolization in patients with unresectable hepatocellular carcinoma. *J Hepatol* 1990; 11:181-184.

90. Lo CM, Ngan H, Tso WK et al: Randomized controlled trial of transarteriallipiodol chemoembolization for unresectable hepatocellular carcinoma.*Hepatology* 2002;35:1164-1171.

91. Malagari K, Chatzimichael K, Alexopoulou E. Trans-arterial chemoembolization of unresectable hepatocellular carcinoma with drug eluting beads: results of an open-label study of 62 patients. CardiovascInterventRadiol 2008;31:269-75.

92. Nolan TR, Grady ED: Intravascular particulate radioisotope therapy: clinical observations of 76 patients with advanced cancer treated with 90-yttrium particles. *Am Surg* 1969; 35:181-188.

93. Mantravadi et al, 1982. Mantravadi RV, et al: Intra-arterial yttrium 90 in the treatment of hepatic malignancy. *Radiology* 1982; 142:783-786.

94. Shepherd FA, et al: A phase I dose escalation trial of yttrium-90 microspheres in the treatment of primary hepatocellular carcinoma. *Cancer* 1992; 70:2250-2254.

95. Goin JE, Salem R, Carr BI et al. Treatment of unresectable hepatocellular carcinoma with intrahepatic yttrium-90 microspheres: factors associated with liver toxicities. J VascIntervRadiol 2005;16:205-13.

96. Livraghi T, et al: Sustained complete response and complete response and complication rates of the radiofrequency ablation of very early hepatocellular carcinoma in cirrhosis: is resection still the treatment of choice?. *Hepatology* 2008; 47:82-89.

97. Poon RT, et al: Effectiveness of radiofrequency ablation for hepatocellular carcinomas larger than 3 cm in diameter. *Arch Surg* 2004; 139:281-287.

98. Chen MS, et al: A prospective randomized trial comparing percutaneous local ablative therapy and partial hepatectomy for small hepatocellular carcinoma. *Ann Surg* 2006; 243:321-328.

99. Lu MD, et al: Surgical resection versus percutaneous thermal ablation for early stage hepatocellular carcinoma: a randomized clinical trial. *Zhonghua Yi XueZaZhi* 2006; 86:801-805

100. Leung TW, Johnson PJ. Systemic therapy for Hepatocellular carcinoma. SeminOncol 2001;28:514-20

101. Edeline J, Raoul JL, Vauleon E, et al. Systemic chemotherapy for hepatocellular carcinoma in non-cirrhotic liver: a retrospective study. World J Gastroenterol 2009;15:713–6.

102. Lau WY, Leung TW, Lai BS et al. Preoperative systemic chemoimmunotherapy and sequential resection for unresectable hepatocellular carcinoma. Ann Surg 2001;233:236-41.

103. Llovet J, Ricci S, Mazzafero V et al. Sorafenib improves survival in advanced hepatocellular carcinoma. Results of a phase III randomized placebo-controlled trial (SHARP trial). J Clinoncol 2007;25:234-98.

104. Kew MC, Popper H. Relationship between hepatocellular carcinoma and cirrhosis. Semin Liver Dis. 1984;4:136–146.

105. Laurent C, Blanc JF, Nobili S, et al. Prognostic factors and long-term survival after hepatic resection for hepatocellular carcinoma originating from noncirrhotic liver. J Am Coll Surg. 2005;201:656–662.

106. Oka H, Tamori A, Kuroki T, Kobayashi K, Yamamoto S. Prospective study of alpha-fetoprotein in cirrhotic patients monitored for the development of hepatocellular carcinoma. Hepatology 1993;19:61-66.

107. Hill PG, Johnson S, Madangopalan N. Serun alpha-fetoprotein and hepatitis B antigen in subjects with hepatoma in south India. Indian J Med Res 1977;65:482-7.

108. Shrager B, Jibara G, Schwartz M, Roayaie S. Resection of Hepatocellular carcinoma without cirrhosis. Ann surg 2012;255:1135-1143.

109. Rossi L, Zoratto F, Papa A, Iodice F, Minozzi M, Frati L et al. Current approach in the treatment of hepatocellular carcinoma. World J GastrointestOncol 2010; 15: 348–359.

110. ThelenA, Benckert C, Tautenhahn HM, Hau HM, Bartels M, lineman et al. Liver resection for hepatocellular carcinoma in patients without cirrhosis. Br J Surg 2013;100:130-37.

111. Worns M, Bosslet T, Victor A, Koch S, Hoppe-Lotichius M, Heise M et al. Prognostic factors and outcomes of patients with hepatocellular carcinoma in non-cirrhotic liver. Scand J gastroenterol 2012;47:718-728.

112. Kumar M, Kumar R, Hissar SS, et al. Risk factors analysis for hepatocellular carcinoma in patients with and without cirrhosis: a case–control study of 213 hepatocellular carcinoma patients from India. J GastroenterolHepatol 2007;22:1104–11.

113. Rayya F, Harms J, Bartels M, et al. Results of resection and transplantation for hepatocellular carcinoma in cirrhosis and noncirrhosis. Transplant Proc. 2008;40:933–935.

APPENDIX

PROFORMA FOR PROGNOSTIC FACTORS AND OUTCOMES AFTER LIVER RESECTION FOR HEPATOCELLULAR CARCINOMA IN NON-CIRRHOTIC, NON-FIBROTIC LIVER

DEMOGRAPHIC DETAILS:

NAME: AGE: SEX: M/F

IP No:

Occupation: Income:

Address:

Date of Admission: Date of Surgery: Date of Discharge:

Length of hospital stay: Post-op: Days Total: Days

FINAL DIAGNOSIS: TREATMENT:

CLINICAL DETAILS:

Symptoms:

Abdominal pain/Abdominal distension/Vomiting/ Fever/chills/

Jaundice/Loss of appetite/ Weight loss/ Hematemesis/ Melena/

Bleeding PR/ Diarrhea/Constipation/ Others:

Duration:

Treatment history: RFA/ TACE

Family history:

Comorbidities: DM/ HT/ IHD/ BA/ COPD/Hypothyroid/ others

Personal History: VEG/ NON-VEG/ SMOKER/ ALCOHOLIC

PHYSICAL FINDINGS:

PALLOR/ICTERUS/LEFT SUPRACLAVICULAR LN

P/A: LIVER/GB/MASS PALPABLE/ FREE FLUID

P/R:

PRE-OPERATIVE INVESTIGATIONS:

Hb%:	PCV:	TC:	DC: P = /L = /E = /M =		
ESR:	Platelets:		PT:	INR:	Sugar:
Urea:	Cr:	Na:	K:	Cl:	Ca:
LFT: TB: DB:		AST:	ALT:	GGT:	SAP:
TP:	ALB:	GLO:	HBsAg:	HCV:	HIV;
CRP:	AFP:	CEA:	Blood group:		Other:

UPPER GI SCOPY: Date: Findings:

LOWER GI SCOPY: Date: Findings:

USG: Date: Findings:

CECT abdomen: Date: Findings:

MRI abdomen: Date: Findings:

PRE-OP TISSUE DIAGNOSIS:

PROVISIONAL DIAGNOSIS:

PROCEDURE DONE:

INTRA-OP EVENTS:

DURATION: mins BLOOD LOSS: ml

TRANSFUSION: PCV: FFP:

Platelets:

INTRA-OP FLUIDS: ml

INTRA-OP COMPLICATIONS:

POST OP COURSE:

POST OP EVENT:	**POD**	**Post-op Investigation**	**POD**
RT removed on:		LFT:	
DT removed on		CRP:	
Urinary catheter:		CBC:	
Oral sips:		RFT:	
Solid diet:		Others:	

POST OP COMPLICATIONS:

INFECTIOUS:	**Yes/ No**	**Grade: (ClaveinDindo)**				
Intra-abdominal collection:						
Post-op liver failure						
Bile leak/bilioma						
Wound infection:						
Pneumonia:						
Sepsis						
NON INFECTIOUS:						
Bleeding						
Ascites						
Cardiac						
Pulmonary:						
Renal:						
Miscellaneous:						

HPE REPORT: Date: No:

Tumor size: Grade: Stage: T N M

Microvascular invasion: Yes/ No Macrovascular invasion: Yes/ No

Capsular invasion: Yes/No Margin status:

Adjoining liver status: Normal liver/Steatosis/

Steatohepatitis/Fibrosis/Cirrhotic

FOLLOW-UP Details: Date: Last follow-up:

Duration: AFP level:

Recurrence: NO YES: Intra-hepatic/ Extra-hepatic

Treatment of recurrence: Re-resection/ RFA/TACE/liver Transplant/

Symptomati

Mortality: Cause Date: Duration after surgery

நோயாளி தகவல் தாள்

கரணை நோயற்ற கல்லீர-ல் ஏற்படும் புற்றுநோய் கட்டிக்கான அறுவை சிகிச்சை
(PROGNOSTIC FACTORS AND OUTCOMES AFTER LIVER RESECTION FOR HEPATOCELLULAR CARCINOMA IN NON-CIRRHOTIC, NON-FIBROTIC LIVER)
குறித்த ஆராய்ச்சிகான ஒப்புதல் படிவம்

நோயாளிகளுக்கான தகவல்:
ஆராய்ச்சியின் நோக்கமும், ஆதாயங்களும்.

உங்கள் பங்கேற்பு திட்டமிடப்பட்டுள்ள இந்த மருத்துவ ஆராய்ச்சி ஆய்வின் நோக்கம்:

உலக புற்றுநோய் தரவரிசையில் கல்லீரல் புற்றுநோய் கட்டி 6-ஆம் இடத்தை வகிறது. ஓர் ஆண்டிற்கு 10,00,000 மக்கள், கல்லீரல் புற்று நோயால் பாதிக்கப்படுகிறார்கள்.

உலக அளவில் பெரும்பாலான கல்லீரல் புற்றுகட்டி, கரணை நோயுள்ள கல்லீர-ல் ஏற்படுவது தான் வழக்கம். ஆனால் இந்தியாவில் சுமார் 40% கல்லீரல் புற்றுகட்டி கரணை நோயற்ற கல்லீர-ல் ஏற்படுகின்றன.

கல்லீரல் புற்றுகட்டிக்கான சிகிச்சை, கல்லீரல் சுருங்கிய நிலையில் உள்ளதா இல்லையா என்று முடிவின் அடிப்படையில் மாறுபடும். ஏனெனில், கரணை நோயுள்ள கல்லீர-ல் ஏற்படும் புற்றுகட்டிக்கு, கல்லீரல் மாற்று அறுவை சிகிச்சையே சிறந்த தீர்வாகும். ஆனால் கரணை நோயற்ற கல்லீர-ல் ஏற்படும் புற்றுகட்டிக்கு, அக்கட்டியை அகற்றும் அறுவை சிகிச்சையே சிறந்த சிகிச்சையாகும்.

இந்த ஆராய்ச்சியின் நோக்கமானது, கரணை நோயற்ற கல்லீர-ல் ஏற்படும் புற்றுகட்டியின் அறிகுறிகளையும், கட்டியின் இயல்புகளையும் அறிவதோடு, இவ்விதமான கல்லீரல் புற்றுகட்டிகளுக்கு செய்யப்படும் கல்லீரல் அறுவைசிகிச்சையின் பலன் மற்றும் பின் விளைவுகளை அறிவதாகும்.

உண்டாகக்கூடிய இடர்கள் :

கரணை நோயற்ற கல்லீர-ல் ஏற்படும் புற்றுக்கட்டிகளுக்கு, கல்லீரல் அறுவைசிகிச்சை என்பது வழக்கில் உள்ள ஒரு நிரந்தர மருத்துவ சிகிச்சைமுறையாகும். இதனால் சிலசமயம் பின்விளைவுகள் ஏற்படுவதோடு, அறிதாக உயிருக்கு ஆபத்து ஏற்பட வாய்ப்புள்ளது.

ஆனால், அவ்வாறு ஏற்படாதிருக்க அனைத்து சிகிச்சைகளும் மேற்கொள்ளப்படும்.

ஆய்வு நடைமுறைகள்:

கரணை நோயற்ற ஏற்படும் கல்லீர-ல் புற்றுகட்டிக்காக அறுவை சிகிச்சை செய்து கொள்ளும் நோயாளிகள் மட்டுமே இந்த ஆய்வில் சேர்ந்து கொள்ளப்படுவார்கள். இந்த ஆராய்ச்சி 24 மாதங்கள் நடைபெறும், உங்கள் சிகிச்சைக்கு தேவையானது தவிர வேறு எந்த பரிசோதனையோ, செய்முறை பயிற்சிகளோ செய்யப்படாது என்று உறுதி அளிக்கிறேன்.

அந்தரங்கத்தன்மை

உங்கள் மருத்துவப் பதிவேடுகள் மிகவும் அந்தரங்கமாக வைத்துக் கொள்ளப்படும் மற்றும் மற்ற பிற மருத்துவர்கள் / விஞ்ஞானிகள் / இந்த ஆய்வின் தணிக்கையாளர்கள் அல்லது ஆராய்ச்சி ஆதரவாளர்களின் பிரதிநிதிகள் ஆகியோரிடமும் அவை வெளிப்படுத்தப்படும். இந்த ஆய்வின் முடிவுகள் அறிவியல் பத்திரிக்கைகளில் பிரசுரிக்கப்படலாம். ஆனால், பெயரை வெளியிடுவது மூலம் நீங்கள் அடையாளம் காட்டப்பட மாட்டீர்கள்.

ஆய்வில் பங்கேற்கும் நோயாளியின் கடமைப் பொறுப்புகள்

உங்களை கவனித்துக் கொள்ளும் மருத்துவருடன் நீங்கள் முழுமையாக ஒத்துழைக்க வேண்டும் என்று உங்களைக் கேட்டுக்கொள்றோம். சிகிச்சையளிக்கும் மருத்துவர் அளிக்கும் அறிவுரைகளை பின்பற்ற வேண்டும் என்றும், என்னென்ன செய்ய வேண்டும், என்னென்ன செய்யக்கூடாது என்று உங்களிடம் கூறப்பட்டுள்ளவற்றி-ருந்து சற்றும் விலகக்கூடாது என்றும் நீங்கள் எதிர் பார்க்கப்படுகிறீர்கள்.

ஆய்வில் உங்கள் பங்கேற்பு மற்றும் உங்கள் உரிமைகள்

இந்த ஆய்வில் உங்கள் பங்கேற்பு தன்னிச்சையானது மற்றும் காரணங்கள் எதையும் கூறாமலேயே நீங்கள் இந்த ஆய்வி-ருந்து எந்த ஒரு நேரத்திலும் விலகிக் கொள்ளலாம். எப்படியிருந்தாலும், உங்கள் உடல் நிலைக்கேற்ப உங்களுக்கு பொருத்தமான சிகிச்சை அளிக்கப்படும். ஆய்வில் பங்கேற்க நீங்கள் மறுப்பதால், அடுத்து வரும் ஆராய்ச்சி ஆய்வுகளில் உங்கள் பங்கேற்பை மறுப்பது போன்ற எந்தவித அபராதமும் விதிக்கப்படாது. உங்களை கவனித்துக் கொள்ளும் மருத்துவருடன் முழுமையாக ஒத்துழைக்க நீங்கள் சம்மதிக்க வேண்டும். எந்த ஒரு நேரத்திலும், நீங்கள் மோசமாக உணர்ந்தாலோ அல்லது வேறு ஏதேனும் உடல் நலக்குறைவு உண்டானாலோ, தயவு செய்து, உங்களை கவனித்து வரும் மருத்துவரிடம் உடனடியாக தெரிவிக்கவும், சிகிச்சை உங்களுக்குப் பொருத்தமாக இருக்காது என்று தோன்றினால் உடனடியாக நிறுத்தப்படும். உங்கள் சம்மதம் இன்றியே கூட ஆய்வு நிறுத்தப்படுவது சாத்தியமே, ஆய்வின் பொழுது ஏதேனும் புதிய தகவல் தெரிய வந்தால், அதைப்பற்றி உங்கள் மருத்துவர் உங்களுக்கு தெரிவிப்பார்.

வேறு ஏதேனும் கேள்விகள் / பிரச்சனைகள் பற்றி நீங்கள் கேட்க விரும்பினால், கீழ்க்கண்ட நபரைத் தொடர்பு கொள்ளவும்.

தனியாகப் பிரிதெடுத்து, ஆய்வில் பங்கேற்பவரிடம் தரப்பட வேண்டும்.

ஆய்வில் பங்கேற்பவர் / சட்டபூர்வமாக
ஏற்கப்பட்ட நபர் கையொப்பம் அல்லது
தெருவிரல் பதிவு

நோயாளி சம்மத படிவம்

கரணை நோயற்ற கல்லீர-ல் ஏற்படும் புற்றுநோய் கட்டிக்கான அறுவை சிகிச்சை (PROGNOSTIC FACTORS AND OUTCOMES AFTER LIVER RESECTION FOR HEPATOCELLULAR CARCINOMA IN NON-CIRRHOTIC, NON-FIBROTIC LIVER) குறித்த ஆராய்ச்சிகான ஒப்புதல் படிவம்

நோயாளியின் பெயர் .....

வயது ..... வருடங்கள் அல்லது பிறந்த தேதி .....

நோயாளியை தொடர்பு கொள்ளும் முகவரி .....

.....

.....

நோயாளியின் தொலைபேசி எண்.

நோயாளியின் இன்சியல்ஸ் ..... பா-னம் ஆண் ..... பெண் .....

		பங்கேற்பவரின் இன்சியல்/பெரு விரல் பதிப்பு
1)	மேல் குறிப்பிடப்பட்டுள்ள ஆய்வின் ..... தேதியிட்ட நோயாளிகளுக்கான செய்தி நான் படித்திருக்கிறேன் மற்றும் புரிந்திருக்கிறேன்/ விவரிக்கப்பட்டுள்ளேன். கேள்விகள் கேட்கவும் அனுமதி வழங்கப்பட்டுள்ளேன் என நான் உறுதி செய்கிறேன்.	
2)	இந்த ஆய்வில் பங்கேற்பது என் சொந்த விருப்பப்படியே என நான் புரிகிறேன். மேலும் என் மருத்துவ சிகிச்சை கவனிப்பு அல்லது சட்ட பூர்வ உரிமைகளுக்கு பாதிப்பு ஏற்படாமல் நான் எந்த நேரத்திலும் விலகிக் கொள்ளலாம் என்பதை புரிகிறேன்.	
3)	எத்திக்ஸ் கமிட்டி மற்றும் ரெகுலேட்டரி அதாரிட்டீஸ்க்கும் நான் இந்த ஆய்வி-ருந்து விலகினாலும் தற்போதைய மற்றும் எதிர்கால இந்த ஆய்வு சார்ந்த என் உடல்நல குறிப்புகளை என் அனுமதியின்றி பார்க்க முடியும் என நான் அறிகிறேன்.	
4)	இந்த ஆய்வில் கிடைக்கப்பெறும் குறிப்புகள் மற்றும் முடிவுகளை உபயோகப்படுத்த தடை செய்ய மாட்டேன் என சம்மதிக்கிறேன். ஆனால் அவைகள் விஞ்ஞானம் சம்மந்தப்பட்டவைகளுக்கு மட்டும் பயன் உள்ளதாக இருக்க வேண்டும்.	
5)	மேற்கூறிய ஆய்வில் பங்கேற்க நான் சம்மதிக்கிறேன்.	

ஆய்வில் பங்கேற்பவர் / சட்டபூர்வமாக
ஏற்கப்பட்ட நபர் கையொப்பம் அல்லது
பெருவிரல் பதிவு

சுய ஒப்புதல் படிவம்

கரணை நோயற்ற கல்லீரல்-ல் ஏற்படும் புற்றுநோய் கட்டிக்கான அறுவை சிகிச்சை (PROGNOSTIC FACTORS AND OUTCOMES AFTER LIVER RESECTION FOR HEPATOCELLULAR CARCINOMA IN NON-CIRRHOTIC, NON-FIBROTIC LIVER) குறித்த ஆராய்ச்சிகான ஒப்புதல் படிவம்

ஆராய்ச்சி நிலையம் : அரசு ஸ்டான்- மருத்துவமனை
சென்னை - 600 001.

பங்கு பெறும் நோயாளியின் பெயர் : வயது :

பங்கு பெறும் நோயாளியின் எண் : பா-னம் : ஆண் ☐ பெண் ☐

நோயாளியின் விலாசம் :

நோயாளி இதனை (✓) குறிக்கவும்.

மேலே குறிப்பிடப்பட்டுள்ள மருத்துவ ஆய்வின் விவரங்கள் எனக்கு விளக்கப்பட்டது. என்னுடைய சந்தேகங்களை கேட்கவும். அதற்கான தகுந்த விளக்கங்களை பெறவும் வாய்ப்பளிக்கப்பட்டது. ☐

நான் என்னை இவ்வாய்வில் தன்னிச்சையாகதான் பங்கேற்க அனுமதிக்கிறேன். எந்த காரணத்தினாலோ எந்த கட்டத்திலும் எந்த சட்ட சிக்கலுக்கும் உட்படாமல் என்னை இவ்வாய்வில் இருந்து விலக்கி கொள்ளலாம் என்றும் அறிந்து கொண்டேன். ☐

இந்த ஆய்வு சம்பந்தமாகவோ, இதை சார்ந்த மேலும் ஆய்வு மேற்கொள்ளும் போதும் இந்த ஆய்வில் பங்குபெறும் மருத்துவர் என்னுடைய மருத்துவ அறிக்கைகளை பார்ப்பதற்கு என் அனுமதி தேவையில்லை என அறிந்து கொள்கிறேன். என்னை ஆய்வில் இருந்து விலகிக் கொண்டாலும் இது பொருந்தும் என அறிகிறேன். ☐

இந்த ஆய்வின் மூலம் கிடைக்கும் தகவல்களையும், பரிசோதனை முடிவுகளையும் மற்றும் சிகிச்சை தொடர்பான தகவல்களையும் மருத்துவர் மேற்கொள்ளும் ஆய்வில் பயன்படுத்திக் கொள்ளவும் அதை பிரசுரிக்கவும் என் முழு மனதுடன் சம்மதிக்கிறேன். ☐

இந்த ஆய்வில் பங்கு கொள்ள ஒப்புக் கொள்கிறேன். எனக்கு கொடுக்கப்பட்ட அறிவுரைகளின்படி நடந்த கொள்வதுடன் இந்த ஆய்வை மேற்கொள்ளும் மருத்துவ அணிக்கு உண்மையுடன் இருப்பேன் என்று உறுதியளிக்கிறேன். என் உடல் பாதிக்கப்பட்டாலோ அல்லது எதிர்பாராத வழக்கத்திற்கு மாறான நோய்க்குறி தென்பட்டாலோ உடனே அதை மருத்துவ அணிக்கு தெரிவிப்பேன் என உறுதி அளிக்கிறேன். ☐

இந்த ஆய்வில் எனக்கு இரத்தம், சிறுநீர், எக்ஸ்ரே, ஸ்கேன் உட்பட அனைத்து பரிசோதனைகளையும் செய்து கொள்ள நான் முழு மனதுடன் சம்மதிக்கிறேன் ☐

பங்கேற்பவரின் கையொப்பம் ..... இடம் ..... தேதி

கட்டைவிரல் ரேகை (இந்த படிவம் படித்து காட்டப்பட்டு புரிந்து கைரேகை அளிக்கின்றேன்)

பங்கேற்பவரின் பெயர் மற்றும் விலாசம் .....

ஆய்வாளரின் கையொப்பம் ..... இடம் ..... தேதி

ஆய்வாளரின் பெயர் .....

MASTER CHART

Name	Age	Sex	IP no	DOA	DOS	DOD	Post-op Stay	Pain abdomen	Pain duration	Mass	Anorexia	Weight loss	Other
Mani	57	M	30613	27.08.10	02.09.10	14.09.10	12	+	3 months	+	+	+	-
Rajendran	58	M	33557	20.09.10	11.10.10	22.10.10	10	+	1 YEAR	-	+	+	-
Udayasooriyan	45	M	42130	27.11.10	16.12.10	04.01.11	18	+	2 month	-	2 months	2 months	-
Varadhan	65	M	39467	06.11.10	23.12.10	25.01.11	31	+	10 days	-	+	+	-
Vellatchi	48	F	24520	13.07.10	04.08.10	16.08.10	12	+	1month	-	+	+	Fever
Yokesh	13	M	17415	18.05.10	31.05.10	28.07.10	29	+	2months	-	+	+	Vomiting
Mariammal	57	F	43562	05.12.11	22.12.11	03.01.12	10	+	7 months	-	+	+	Vomiting
Valli	30	F	32527	08.09.11	26.09.11	12.10.11	16	+	6 months	-	+	+	-
Vasuki	59	F	6265	20.02.12	19.03.12	09.04.12	20	+	5month	+	+	+	Fever
Kumar	30	M	5863	16.02.12	23.02.12	19.02.12	26	+	1MONTH	-	+	+	-
Rajendran	50	M	32678	12.01.11	22.01.11	02.02.11	14	+	3months	-	+	+	-
Srinivasan	16	M	32760	19.07.10	25.08.12	09.09.12	14	+	1month	+	+	+	-
Vijaya	33	F	8982	17.03.11	24.05.11	03.06.11	9	+	1month	-	-	-	Bleeding PR
Kattari	48	M	52077	28.12.10	05.01.11	07.02.11	28	+	1 month	-	+	+	Vomiting
Sundaram	50	M	9648	18.03.11	18.04.11	29.04.11	11	+	1 month	-	+	+	Fever
Mani sathyamoorthy	53	F	3584	20.06.10	22.07.10	06.08.10	14	+	3 months	+	+	+	?
Kanagarajan	52	M	51093	19.12.10	09.01.11	21.01.11	12	+	3 months	-	+	+	-
Arumugam	58	M	45356	23.10.10	07.11.10	16.11.10	10	+	1 month	-	+	+	-
Maharajan	56	m	32060	08.09.10	30.09.10	19.10.10	20	+	1 month	-	+	+	-
Mani	54	F	34789	06.05.11	25.05.11	07.06.11	12	+	2months	-	+	+	-
Mohanambal	60	F	31697	02.09.11	13.10.11	25.10.11	12	+	1month	-	+	+	Pain abdomen
Padma	48	F	11918	06.04.11	26.04.11	09.05.11	13	+	1month	+	+	+	Vomiting
Theresa	31	F	55093	06.12.12	30.12.12	15.01.12	13	+	1month	-	+	+	Vomiting
Vatchala	64	F	21357	18.06.10	08.07.10	30.07.10	35	+	2 month	+	+	+	-
Devaraj	23	M	21785	09.08.10	18.08.10	27.08.10	10	+	2months	-	+	+	-
Shanmugam	52	M	21686	21.06.10	15.07.10	07.08.10	22	+	6 months	-	2months	2 months	
Arulappadurai	77	M	16028	09.05.11	11.05.11	25.05.11	18	+	1month	-	+	+	-
Subbiah	53	M	17984	24.05.11	08.06.11	24.06.11	16	+	3months	-	+	+	-
Rajendran	55	M	42371	24.11.11	07.12.11	21.12.11	14	+	10 days	-	+	+	Fever - 10days
Saravanan	52	M	30893	25.08.11	14.09.11	30.09.11	22	+	6 months	+	2months	2 months	-

Name	Alcohol	Smoker	Comorbid	Anaemia	Jaundice	Ascites	Hepatomegaly	HB	TC	NLR	ESR	PLATELETs	PT	PTI
Mani	+	+		+	-	-	+	8.6	8000	4.41	38	7	14	100
Rajendran	+	+	HT	+	-	-	-	9.3	9100	2.03	90	5.86	14	100
Udayasooriyan	-	-	DM	-	-	-	-	11	8200	3.09	52	3	14	100
Varadhan	-	-	-	-	-	-	+	9.6	6000	2.6	22	1.42	14	100
Vellatchi	-	-	DM	-	-	-	-	11.3	7000	2.33	24	3.09	14	100
Yokesh	-	-	-	-	-	-	+	10.4	13300	2.33	25	6.8	15	93.33
Mariammal	-	-	DM	-	-	-	+	9.5	8000	2.79	34	2.25	14	100
Valli	-	-	-	-	-	-	+	8.8	7900	2.32	34	6.69	14	100
Vasuki	-	-	HT	-	-	-	-	12.7	7600	1.09	8	2.73	14	100
Kumar	-	-	-	-	-	-	-	14	6400	2.46	16	5.19	14	100
Rajendran	+	+	-	-	-	-	-	10.1	8500	1.71	30	3.07	14	100
Srinivasan	-	-	-	-	-	-	+	13	8100	2	60	4.89	14	100
Vijaya	-	-	-	-	-	-	+	9.9	8700	2.16	80	3.11	14	100
Kattari	+	+	-	-	+	-	+	9.3	8600	7.33	120	2.64	18	77.77
Sundaram	-	-	-	-	-	-	-	12.5	10100	6.91	30	1.96	14	100
Mani sathyamoorthy	-	-	-	-	-	-	+	10	6500	1.9	80	6.23	16	87.5
Kanagarajan	-	-	-	-	-	-	+	9.4	2200	1.25	60	5.7	15	93.33
Arumugam	+	+	HT	+	-	-	-	9.3	9100	2.03	90	5.86	14	100
Maharajan	+	+	DM	-	-	-	-	11.6	8300	1.41	20	2.74	14	100
Mani	-	-	-	-	-	-	+	11.6	6800	1.64	32	1.9	14	100
Mohanambal	-	-	-	-	-	-	+	11.3	7200	3.13	30	2.36	15	93.3
Padma	-	-	HT	-	-	-	+	13.2	7600	1.42	8	2.61	14	100
Theresa	-	-	-	-	-	-	-	10.4	15000	4.41	32	6.06	14	100
Vatchala	-	-	DM	-	-	-	+	12	11100	1.96	26	2.5	14	100
Devaraj	-	-	obese	-	-	-	-	11	7890	2.32	33	1.75	15	93.3
Shanmugam	+	+	Obese	-	+	-	+	8.9	6700	2.91	36	4.1	14	100
Arulappadurai	-	+	DM	-	-	-	-	8.5	13500	1.14	42	1.97	17	82.35
Subbiah	-	-	obese	-	-	-	-	13.4	7800	3.18	36	1.85	14	100
Rajendran	+	-	DM	-	-	-	+	12.2	8500	6.07	24	1.98	14	100
Saravanan	+	+	DM	-	-	-	+	8.9	6700	2.91	36	4.1	14	100

Name	INR	Sugar	Urea	Cr	Na	K	Cl	TB	AST	ALT	GGT	SAP	ALB	HBV	HCV	AFP	Pre-op Biopsy
Mani	1	67	30	1.15	132	4.2	100	0.9	65	78	41	174	3.7	-	-	6.9	-
Rajendran	1	90	13	0.68	146	3.84	103	0.6	54	47	63	255	3.1	-	-	6.8	-
Udayasooriyan	1	125	21	0.83	135	4.3	100	0.74	67	45	56	246	3.1	+	-	4.44	-
Varadhan	1	115	28	1.09	133	4.1	96	1	498	33	357	617	3.2	-	-	3.14	+
Vellatchi	1	139	22	0.75	141	4.1	102	0.9	100	56	11	214	2.8	+	-	>3000	-
Yokesh	1.1	81	19	0.7	141	4.9	105	0.7	48	31	43	214	3.2	-	-	800	-
Mariammal	1	143	50	1.54	140	4.7	104	0.48	26	24	23	248	4.1	-	-	0.69	+
Valli	1	109	15	0.5	125	4.7	90.5	1.08	37	42	17	196	3.8	-	-	1.67	-
Vasuki	1	261	19	0.81	139	4.45	101	0.48	21	32	106	337	3.7	-	-	1.9	-
Kumar	1	116	19	1.1	138	3.9	100	1.2	31	41	44	187	3.8	-	-	432	-
Rajendran	1	102	29	1.19	137	4.1	99	0.8	26	8	10	134	3.6	-	-	1.6	-
Srinivasan	1	107	22	1	140	5.5	104	0.89	50	19	31	187	4.9	-	-	0.3	-
Vijaya	1	87	35	0.6	137	4	97	1.2	115	22	42	188	3.4	-	-	11.3	-
Kattari	1.4	88	20	0.7	132	4.13	98.2	3.6	80	36	39	202	2.8	-	-	32476	-
Sundaram	1	71	22	1	136	4.2	100	0.45	35	19	16	172	2.7	-	-	456	-
Mani sathyamoorthy	1.3	111	24	0.6	142	3.76	101	0.8	38	21	45	198	2.6	-	-	23	-
Kanagarajan	1.1	175	13	0.5	135	5.03	102	1.3	89	53	54	307	3.7	-	-	89	-
Arumugam	1	90	13	0.68	146	3.84	103	0.6	54	47	63	255	3.1	-	-	6.8	-
Maharajan	1	268	14	0.58	142	4.46	103	0.9	54	64	48	235	3.5	-	-	6.9	-
Mani	1	110	20	0.7	141	4.4	102	1.2	56	48	320	399	3.4	-	-	2.07	-
Mohanambal	1.1	86	18.4	0.93	140.5	4.38	105	0.25	26	20	42	149	4	-	-	6.78	-
Padma	1	129	17.1	0.78	139	4.2	101	1.33	143	173	1050	610	4.5	-	-	11.9	-
Theresa	1	144	18	0.8	143	3.7	100	1	26	40	54	381	3.4	-	-	1.2	-
Vatchala	1	144	18.8	0.45	139	4.5	105	1	114	59	147	209	3.2	-	-	41.8	-
Devaraj	1.1	95	21	0.7	141	3.9	101	1	22	16	56	211	4.2	-	-	128	-
Shanmugam	1	110	17.9	0.8	131	3.9	95.1	3.4	151	56	31	381	3.1	-	-	67	-
Arulappadurai	1.2	70	20	0.4	144	4	103	1.2	220	156	16	85	2.5	-	-	1.33	+
Subbiah	1	91	33	1	141	4.7	102	0.7	58	41	53	173	3	+	-	57.21	-
Rajendran	1	194	20	0.74	133	5.44	98	0.73	83	47	59	311	3.6	+	-	13.9	-
Saravanan	1	110	17.9	0.8	131	3.9	95.1	3.4	151	56	31	381	3.1	-	-	67	-

Name	Surgery	Major resection	Minor	LIVER	DEPO-SITS	FF	Blood loss	Blood Tx	Duration	Complication
Mani	Rt Hepatectomy	+	-	Normal	-	-	100	-	2	-
Rajendran	Lt. Hepatectomy	+	-	Normal	-	-	150	-	2.5	-
Udayasooriyan	Rt Hepatectomy	+	-	nodule in lt lobe &seg 6	-	-	200	-	2.5	-
Varadhan	Extended Right Hepatectomy	+	-	Normal	-	-	300	-	3.5	+
Vellatchi	Rt Hepatectomy	+	-	normal	-	+	250	-	2.5	-
Yokesh	Extended right hepatectomy with excision of diaphragm and mesh repair	+	-	Normal	-	-	200	-	2.5	+
Mariammal	Lt. Hepatectomy	+	-	normal	-	-	100	-	2	+
Valli	Rt Hepatectomy	+	-	normal	-	-	150	-	2	-
Vasuki	Lt. Hepatectomy	+	-	NORMAL	-	-	200	-	2.5	+
Kumar	Left lateral segmentectomy	-	+	Normal	-	-	250	-	3	+
Rajendran	Lt. Hepatectomy	+	-	Normal	-	-	200	-	2.5	+
Srinivasan	Rt Hepatectomy	+	-	Normal	-	-	100	-	2	-
Vijaya	Extended Right Hepatectomy	+	-	Normal	-	-	150	-	2	+
Kattari	Rt Hepatectomy	+	-	Normal	-	-	100	-	2	+
Sundaram	Lt. Hepatectomy	+	-	Normal	-	-	250	-	3	-
Mani sathyamoorthy	Bisegmentectmy (segment VI, VIII)	-	+	Normal	-	-	300	-	3.5	+
Kanagarajan	Rt Hepatectomy	+	-	Normal	-	-	100	-	2	-
Arumugam	Extended Left Hepatectomy	+	-	Normal	-	-	150	-	2	-
Maharajan	Extended Right Hepatectomy	+	-	Normal	-	-	175	-	2.5	+
Mani	Lt. Hepatectomy	+	-	Normal	-	-	300	-	3.5	+
Mohanambal	Rt Hepatectomy	+	-	Normal	-	-	300	-	3	-
Padma	Central Hepatectomy	+	-	Normal	-	-	150	-	2	-
Theresa	Rt Hepatectomy	+	-	Normal	-	-	250	-	2.5	-
Vatchala	Extended Right Hepatectomy	+	-	Normal	-	-	250	-	2	+
Devaraj	Bisegmentectomy (segment 5 & 6)	-	+	Normal	-	-	720	-	3	-
Shanmugam	Rt. Hepatectomy with Lt metastasectomy with excision of part of diaphragm	+	-	Normal	-	+	300	1 U	3	+
Arulappadurai	Non Anatomical Resection of segment V and VI with HCC	-	+	Normal	-	-	150	-	1.5	+
Subbiah	Non Anatomical Resection	-	+	Normal	-	-	100	-	1	+
Rajendran	Rt Hepatectomy	+	-	Normal	-	-	250	-	2.5	-
Saravanan	Rt. Hepatectomy with Lt metastasectomy with excision of part of rt dome	+	-	Normal	-	+	300	1 U	3	+

Name	IA collection	Liver insufficiency	Rena failure	Chest infection	Wound infection	Bleeding	Pancreatitis	Bile leak	sepsis	Pulmonary embolism	Others	Solitary	Multiple	Size
Mani	-	-	-	-	-	-	-	-	-	-	-	+	-	15x15
Rajendran	-	-	-	-	-	-	-	-	-	-	-	+	-	20x12
Udayasooriyan	-	-	-	-	-	-	-	-	-	-	-	+	-	25x10x5
Varadhan	-	-	-	+	+	-	-	-	-	-	-	+	-	13x12
Vellatchi	-	-	-	-	-	-	-	-	-	-	-	+	-	13x12
Yokesh	+	+	-	-	+	-	-	+	-	-	-	+	-	12x10
Mariammal	-	-	-	-	-	-	-	-	-	-	High BP-NTG drip, Dyselectrolytemia	+	-	20x15x5
Valli	-	-	-	-	-	-	-	-	-	-	-	+	-	12x10
Vasuki	+	-	-	+	+	-	-	-	+	-	-	+	-	15x10
Kumar	-	-	-	+	-	-	-	-	-	-	-	+	-	14x12
Rajendran	+	-	+	-	-	-	-	-	-	-	-	-	+	6X6
Srinivasan	-	-	-	-	-	-	-	-	-	-	-	-	+	6X5
Vijaya	+	-	-	-	-	-	-	-	-	-	-	+	-	12x14
Kattari	-	-	-	-	+	-	-	-	+	-	-	+	-	10x12
Sundaram	-	-	-	-	-	-	-	-	-	-	-	+	-	12x14
Mani sathyamoorthy	-	-	-	-	-	-	-	-	+	-	-	+	-	16x12
Kanagarajan	-	-	-	-	-	-	-	-	-	-	Edema	+	-	13x12
Arumugam	-	-	-	-	-	-	-	-	-	-	-	+	-	15x15
Maharajan	+	-	-	-	-	-	-	+	-	-	-	+	-	5x6cm
Mani	-	-	-	-	-	-	-	-	-	-	-	+	-	20x20cm
Mohanambal	-	-	-	-	-	-	-	-	-	-	-	+	-	20x15
Padma	-	-	-	-	-	-	-	-	-	-	-	+	-	10x8
Theresa	-	-	-	-	-	-	-	-	-	-	-	+	-	8x6cm
Vatchala	+	-	-	+	+	-	-	-	+	-	-	-	+	5X5
Devaraj	-	-	-	-	-	-	-	-	-	-	-	+	-	10x10cm
Shanmugam	-	+	-	-	-	-	-	-	-	-	-	-	+	8x6cm
Arulappadurai	-	-	-	-	-	-	-	+	-	-	-	-	+	6X5
Subbiah	-	+	-	-	-	-	-	-	+	-	Dyselectrolytemia	-	+	20x15x7
Rajendran	-	-	-	-	-	-	-	-	-	-	-	+	-	15x17x7
Saravanan	-	+	-	-	+	-	-	-	-	-	-	-	+	19x16

Name	Encapsulated	Differentiation	Microvascular invasion	macrovascular invasion	Capsular invasion	Margin	Adjoining liver	Steatosis	Steatohepatitis	Fibrosis	Cirrhosis
Mani	+	II	-	-	-	-	normal	-	-	-	-
Rajendran	+	I	-	-	-	-	normal	-	-	-	-
Udayasooriyan	+	III	-	-	-	-	Normal	-	-	-	-
Varadhan	+	II	-	-	-	-	normal	-	-	-	-
Vellatchi	+	II	+	-	+	-	Steatosis& Periportal inflammation	+	-	-	-
Yokesh	-	III	+	-	-	-	normal	-	-	-	-
Mariammal	+	I	+	-	+	+	Steatosis	+	-	-	-
Valli	-	I	-	-	-	-	Normal	-	-	-	-
Vasuki	+	II	-	-	-	-	normal	-	-	-	-
Kumar	+	i	-	-	-	-	normal	-	-	-	-
Rajendran	+	II	+	-	-	+	normal	-	-	-	-
Srinivasan	-	II	+	-	-	-	Normal	-	-	-	-
Vijaya	+	III	+	-	+	+	Normal	-	-	-	-
Kattari	-	III	+	-	-	-	normal	-	-	-	-
Sundaram	-	I	-	-	-	-	normal	-	-	-	-
Mani sathyamoorthy	-	III	+	-	-	-	normal	-	-	-	-
Kanagarajan	-	I	-	-	-	-	normal	-	-	-	-
Arumugam	+	I	-	-	-	+	normal	-	-	-	-
Maharajan	+	I	-	-	-	-	normal	-	-	-	-
Mani	-	I	-	-	-	-	normal	-	-	-	-
Mohanambal	+	I	-	-	-	-	normal	-	-	-	-
Padma	+	III	+	-	+	-	normal	+	-	-	-
Theresa	+	II	-	-	-	-	normal	-	-	-	-
Vatchala	+	I	-	-	-	-	Steatosis	+	-	-	-
Devaraj	+	I	+	-	-	+	normal	-	-	-	-
Shanmugam	+	II	+	-	-	-	Steatosis	+	-	-	-
Arulappadurai	-	III	+	-	-	+	normal	-	-	-	-
Subbiah	_	III	+	-	-	+	normal	-	-	-	-
Rajendran	+	I	+	-	+	+	normal	-	-	-	-
Saravanan	-	III	+	-	-	-	normal	-	-	-	-

Name	1 year	Recurrence	2 year	Recurrence3	3 year	Recurrence4	Survival days	Recurrence days	Last Follow-up
Mani	alive	-	alive	-	alive	+	36	29	21.02.13
Rajendran	alive	-	alive	-	Alive	-	30	30	04.01.13
Udayasooriyan	alive	-	alive	-	alive	-	34	34	25.02.13
Varadhan	alive	-	alive	-	alive	+	32	26	22.02.13
Vellatchi	alive	+	dead	+	dead	+	25	24	05.09.12
Yokesh	alive	-	alive	+	dead	+	33	27	11.02.13
Mariammal	alive	-	alive	-	-	-	24	24	26.12.12
Valli	alive	-	alive	-	alive	-	22	22	23.01.13
Vasuki	alive	-	alive	-	-	-	12	12	09.02.13
Kumar	alive	-	-	-	-	-	12	12	11.02.13
Rajendran	alive	-	-	-	-	-	12	12	07.02.13
Srinivasan	alive	+	dead	+	dead	+	23	21	13.07.12
Vijaya	alive	+	dead	+	dead	+	25	11	09.06.12
Kattari	dead	+	dead	+	dead	+	12	9	22.12.11
Sundaram	alive	-	alive	-	alive	-	24	24	07.01.13
Mani sathyamoorthy	dead	+	dead	+	dead	+	14	10	19.08.11
Kanagarajan	alive	-	alive	-	alive	-	36	36	14.02.13
Arumugam	alive	-	alive	-	alive	-	36	36	05.02.13
Maharajan	alive	-	alive	-	alive	-	36	36	07.02.13
Mani	alive	-	alive	-	alive	-	24	24	25.02.13
Mohanambal	alive	-	alive	-	alive	-	22	22	19.01.13
Padma	alive	-	alive	+	alive	+	18	20	22.01.13
Theresa	alive	-	alive	-	alive	-	20	20	18.02.13
Vatchala	alive	-	alive	+	alive	+	36	18	29.01.13
Devaraj	dead	NA	Dead	NA	Dead	NA	12	11	03.03.11
Shanmugam	alive	+	dead	+	dead	+	25	11	27.07.12
Arulappadurai	dead	+	dead	+	dead	+	13	10	19.06.12
Subbiah	alive	+	dead	+	dead	+	19	12	09.01.13
Rajendran	alive	-	alive	-	-	-	24	24	01.02.13
Saravanan	alive	+	dead	+	dead	+	25	12	29.08.12